The Link Between Obesity and Asthma

aanc 2010 North Carolina Asthma Summit

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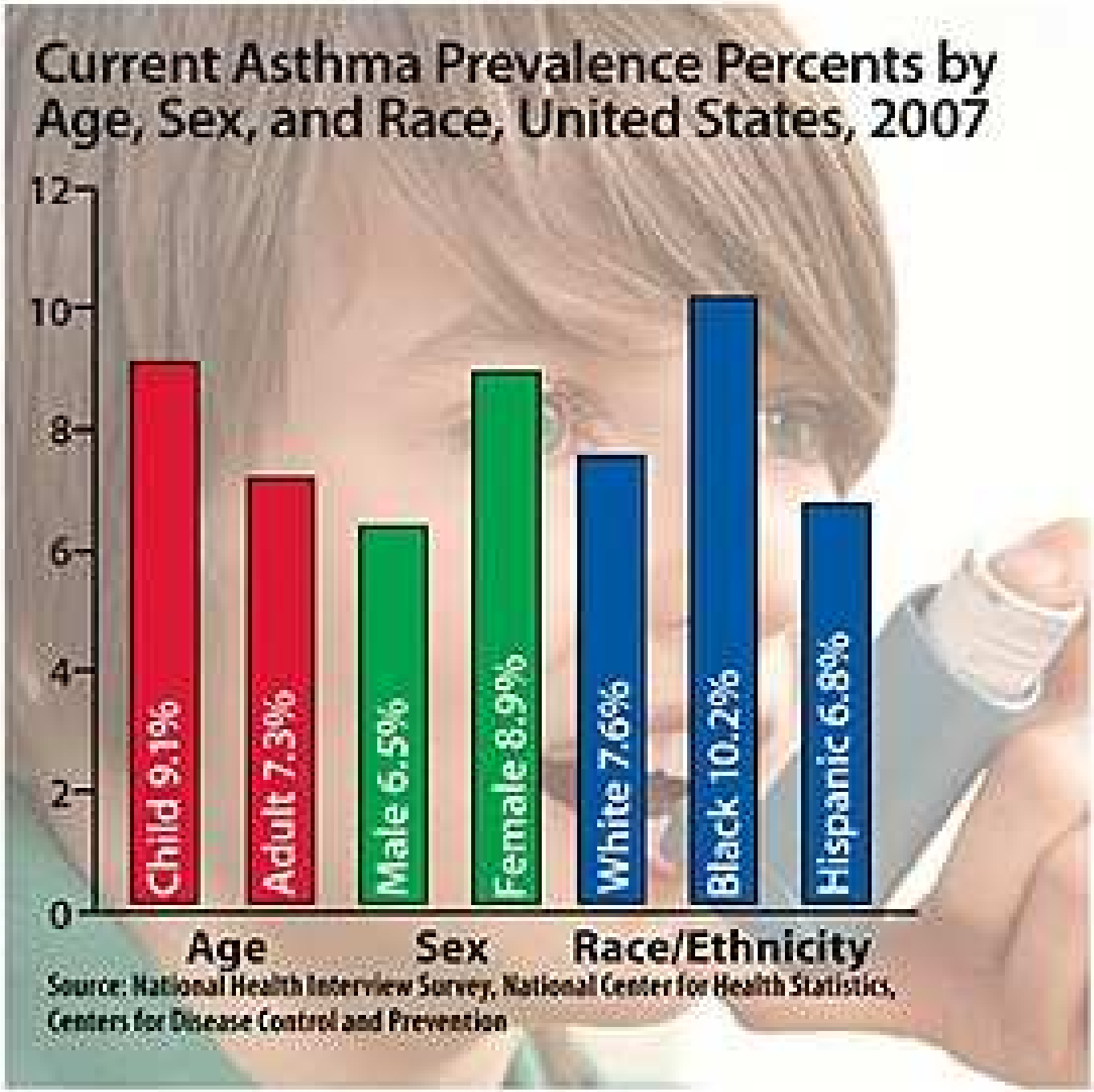
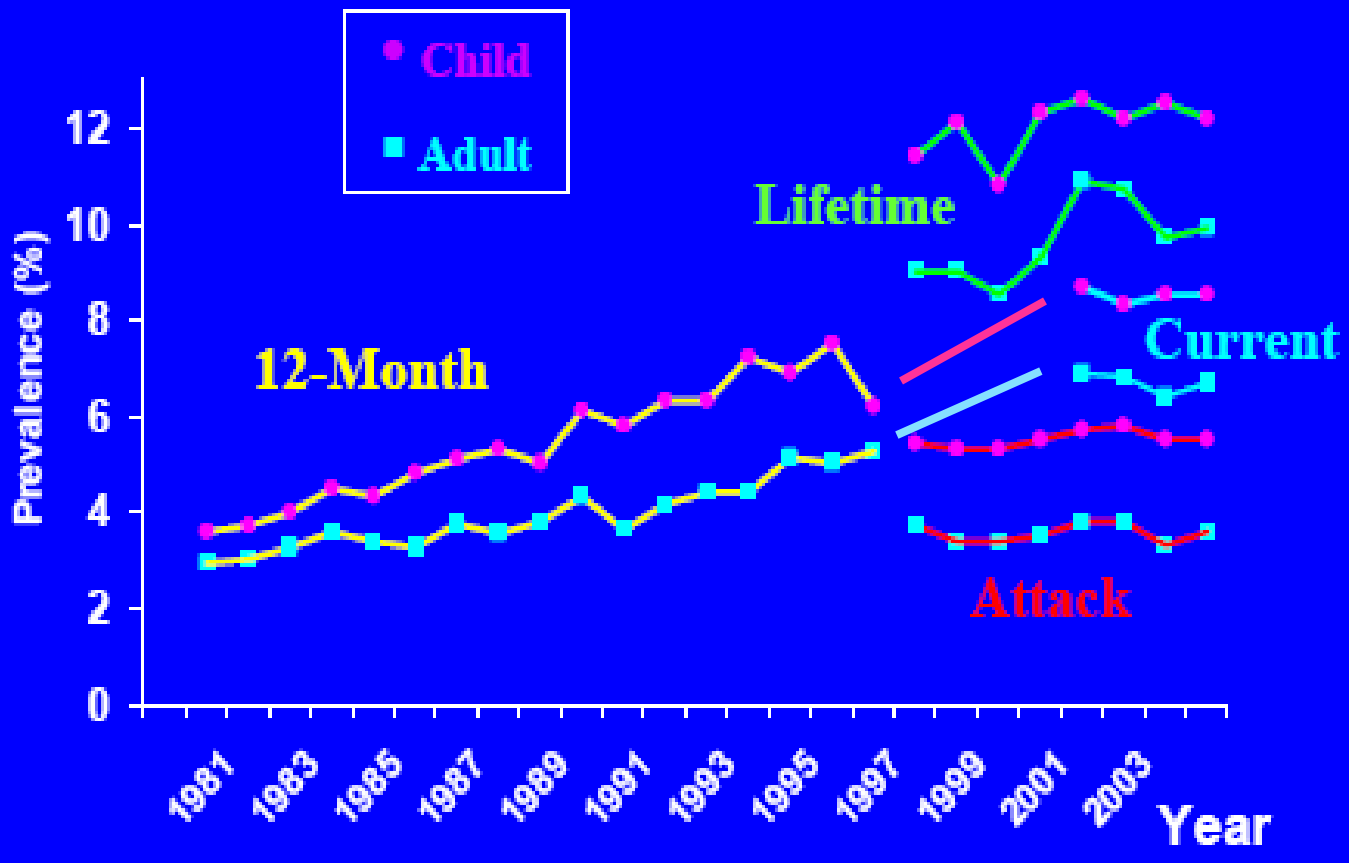
Brody School of Medicine


Current Asthma Prevalence Percents by Age, Sex, and Race, United States, 2007
12
10
8
6
4
2
0
Child 9.1%
Adult 7.3%
Male 6.5%
Female 8.9%
White 7.6%
Black 10.2%
Hispanic 6.8%
Age
Sex
Race/Ethnicity
Source: National Health Interview Survey, National Center for Health Statistics, Centers for Disease Control and Prevention

Child and Adult Asthma Prevalence

United States, 1980-2004



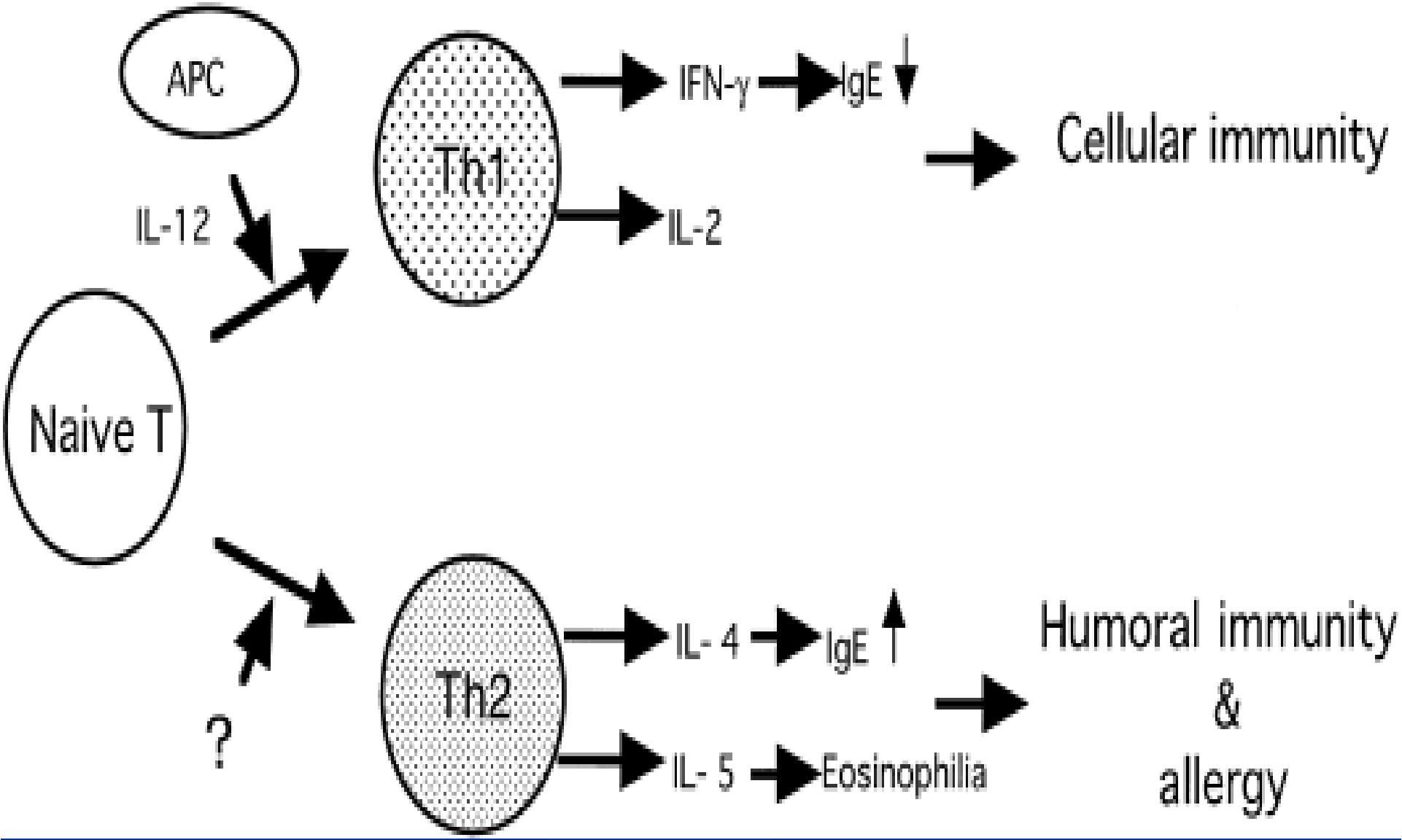
Source: National Health Interview Survey; National Center for Health Statistics

CDC

Proposed causes of rising asthma prevalence.

- Air pollution or other environmental exposures
- Environmental tobacco smoke
- Smaller family size
- Decreased exposure to infectious diseases

Th2 predominance results in atopy and asthma



Proposed causes of rising asthma prevalence.

- Air pollution
- Environmental tobacco smoke
- Smaller family size
- Decreased exposure to infectious diseases
- Obesity
  - Co-incident rise in both obesity and asthma
  - Dietary influences
  - Gastro-esophageal reflux
  - Disordered sleep breathing
  - Mechanical factors
  - Adipokine/cytokine hormonal
  - Genetic/epigenetic

Objectives

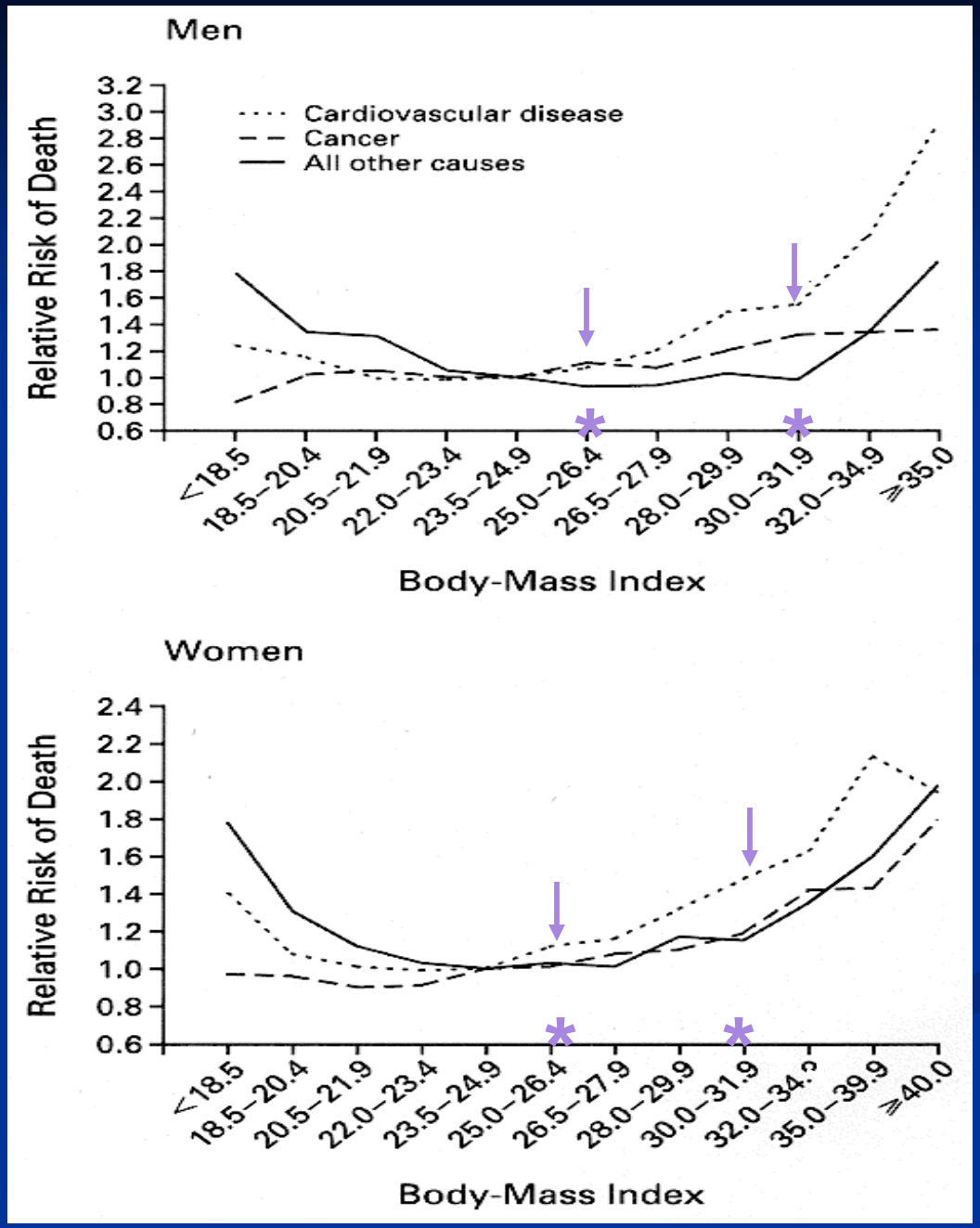
- Evaluate the epidemiologic evidence connecting obesity and asthma
- Understand that weight loss mitigates asthma in obese adults
- Appreciate potential mechanistic links between obesity and asthma
- Know that obesity influences response to asthma treatment

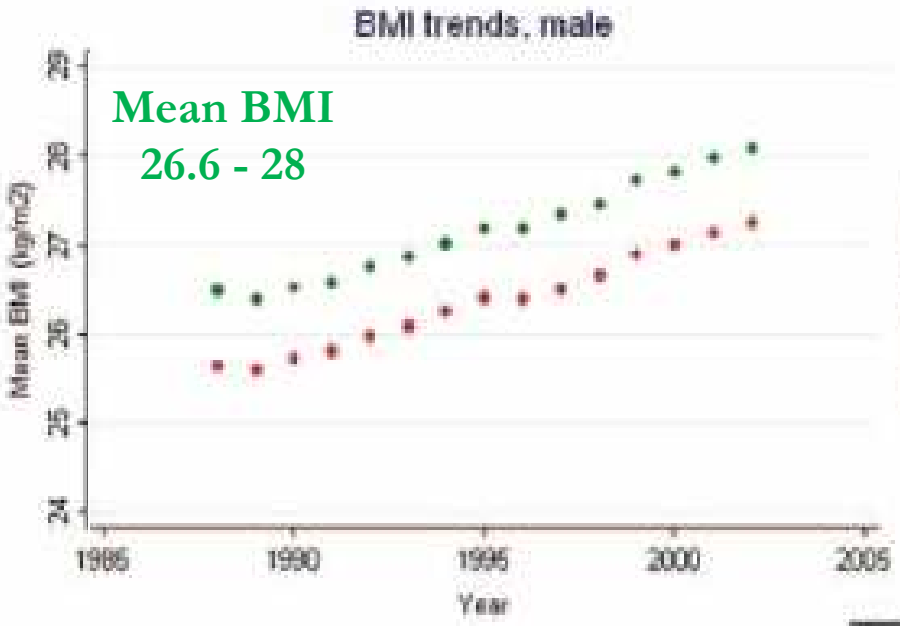
Definition of Obesity: Adults

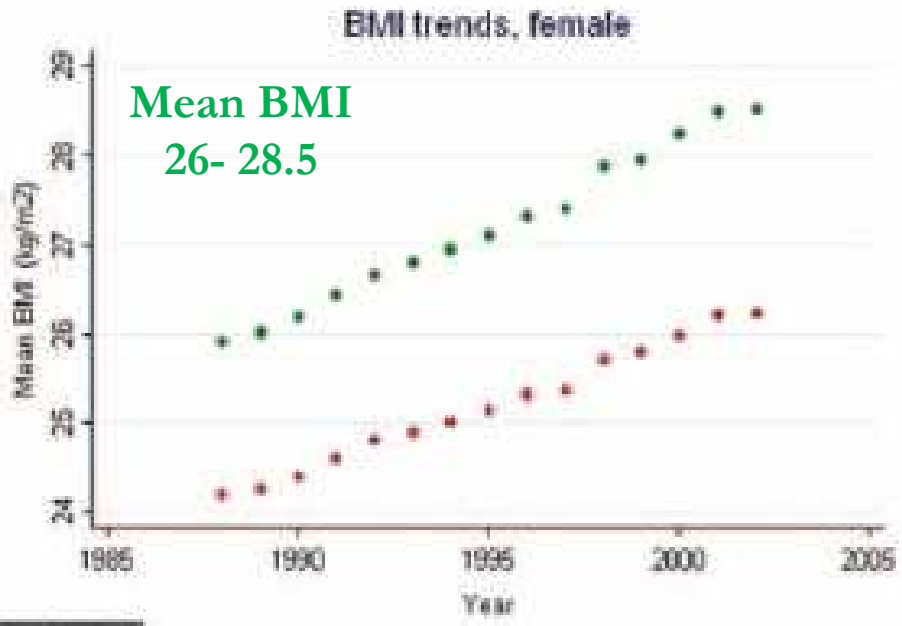
- Body mass index (BMI)
  - Weight (kg)/ [height (m)]^2
  - Weight (lbs) x 703 /[height (in)]^2
- Adult criteria (WHO and NIH)
  - < 18.5 kg/m^2 underweight
  - 18.5 - 24.9 normal weight
  - 25 – 29.9 overweight
  - ≥ 30 obese
  - ≥ 40 extreme obesity

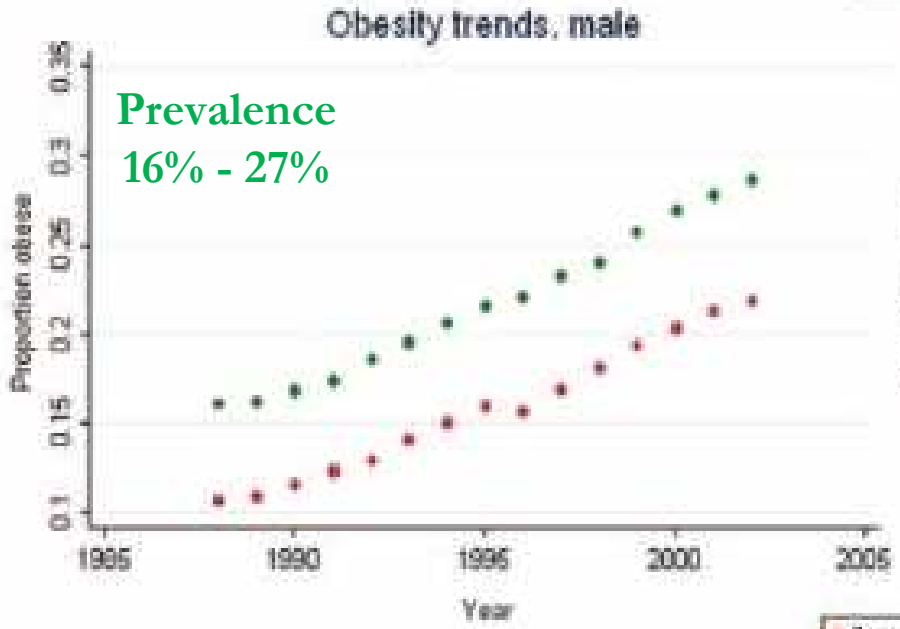
Relative Risk of Death vs. BMI

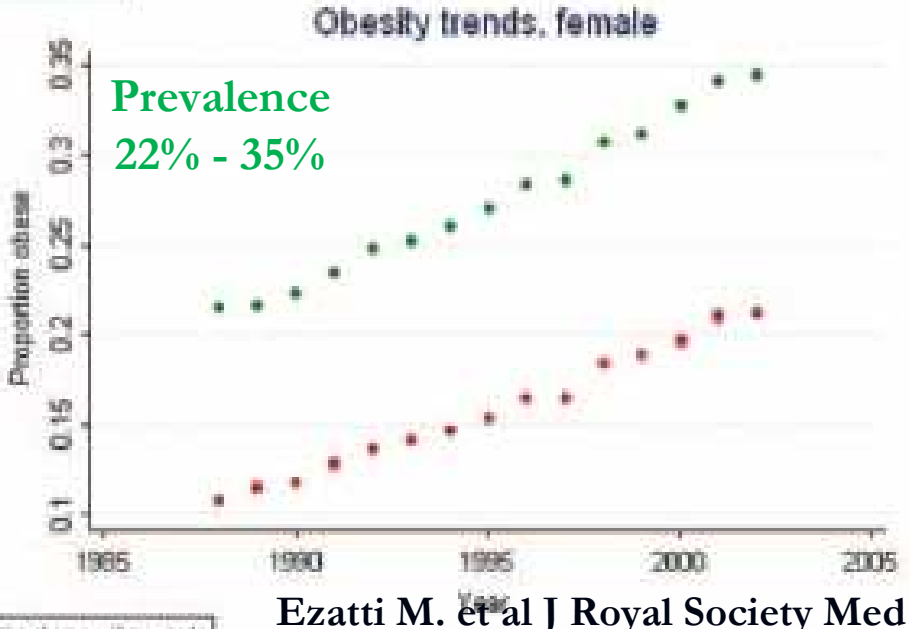
Calle EE et al
NEJM 1999;341:
1097-1105







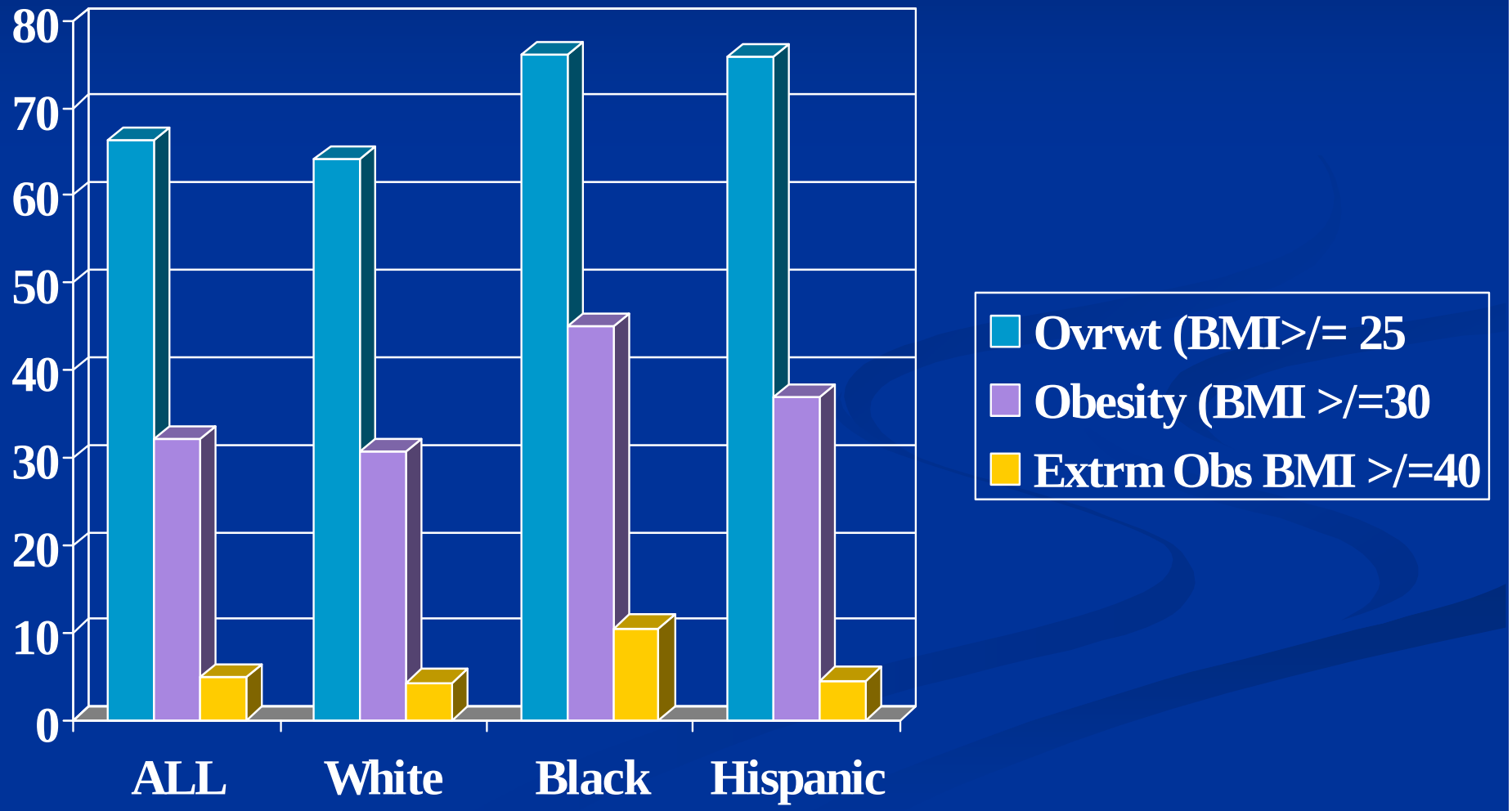




Ezatti M. et al J Royal Society Med 2006;99:250-7

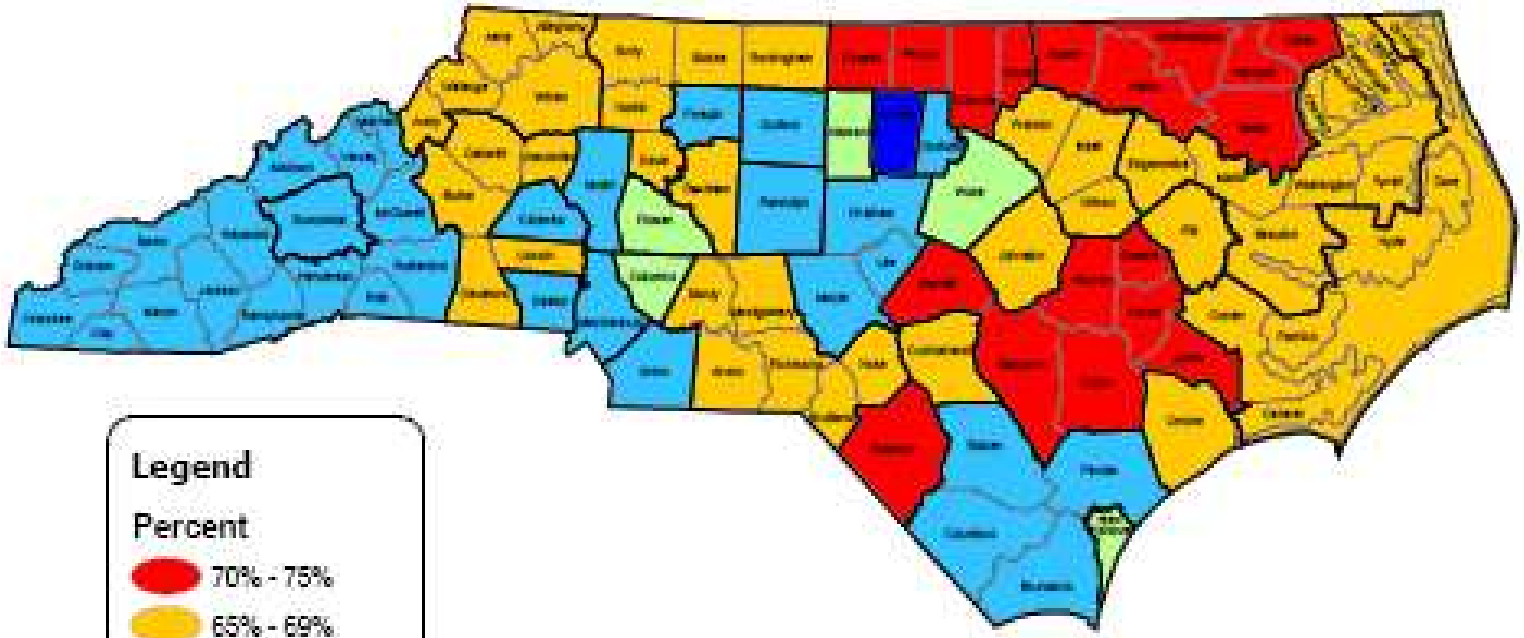
Prevalence of Overweight, Obesity and Extreme Obesity in Adults

(NHANES 2003-2004 JAMA 2006;295:1549-55)



Percentage of North Carolina Adults Who Are Overweight or Obese

BMI* ≥25



Legend

Percent

- 70% - 75%
- 65% - 69%
- 62% - 64%
- 57% - 61%
- 47% - 56%
- BRFSS Regions
- County Boundary

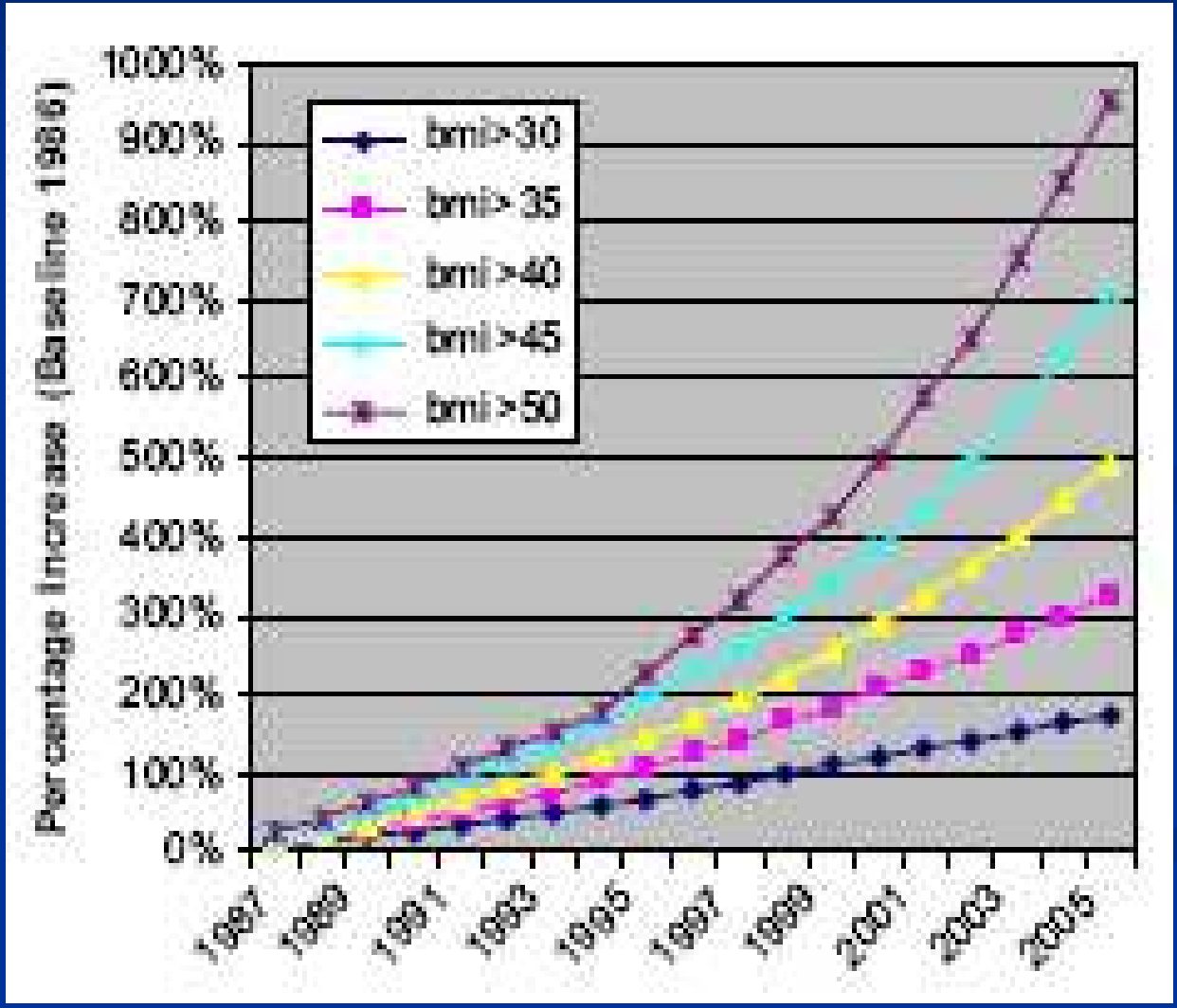
Source: 2006 Behavioral Risk Factor Surveillance System (BRFSS)

*Body mass index is computed as weight in kilograms divided by height in meters squared:(kg/ m2). BMI is an intermediate variable used in defining overweight and obesity. Underweight=BMI less than 18.5, Recommended Range=BMI 18.5 to 24.9, Overweight=BMI 25.0 to 29.9 and Obese= BMI greater than 30.0

NC State Center for Health Statistics

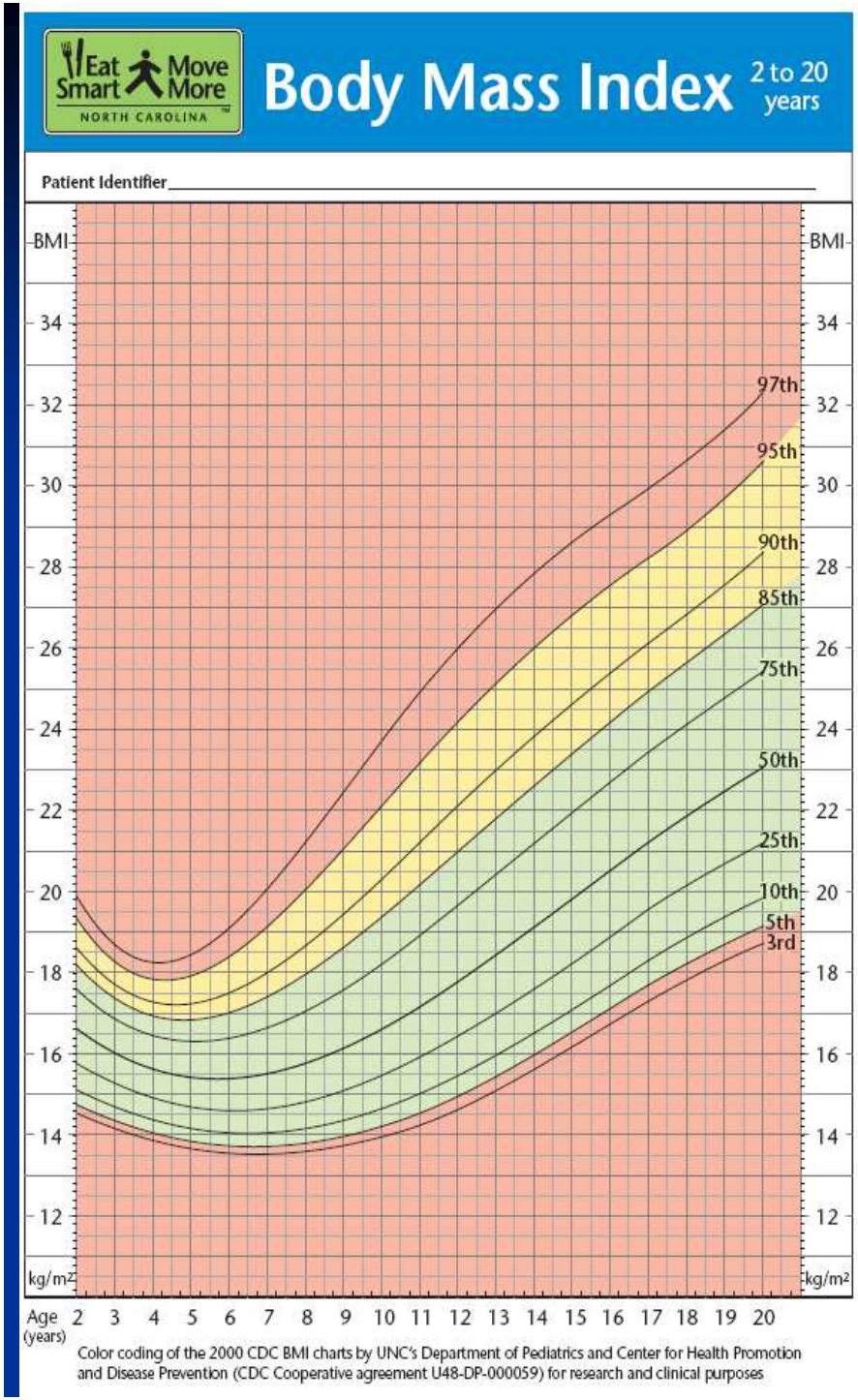
Extreme obesity: the epidemic within an epidemic

Strum R. Public Health 2006;121:492-496.



Definition of Obesity: Children

- Body mass index (BMI)
  - Weight (kg)/ [height (m)]^2
- Age and gender specific norms (CDC)
  - www.cdc.gov
- Definitions:
  - BMI < 5th percentile: underweight
  - BMI $\geq$ 5th but $\leq$ 85th 'tile normal
  - BMI > 85th but < 95th 'tile overweight
  - BMI $\geq$ 95th obese
  - BMI $\geq$ 99th extreme obesity



BOYS

To calculate BMI:

Kilograms and meters:
weight (kg) / [height (m)]^2

Pounds and inches:
weight (lb) / [height (in)]^2 x 703

BOYS: 99th percentile cut-points

AGE	BMI
5	20.1
6	21.6
7	23.6
8	25.6
9	27.6
10	29.3
11	30.7
12	31.8
13	32.6
14	33.2
15	33.6
16	33.9
17	34.4

From National Initiative for Children's Healthcare Quality (www.nichq.org)

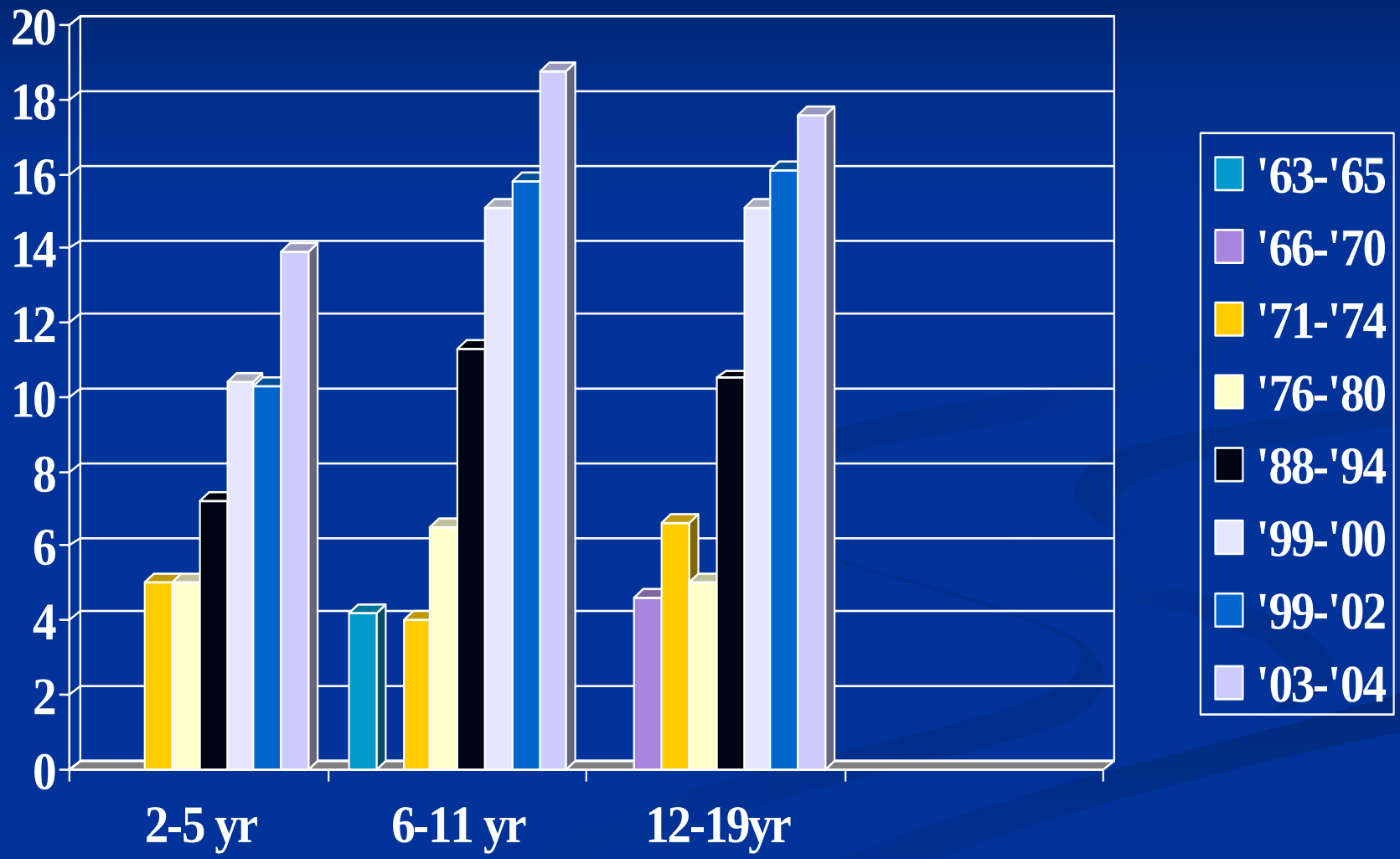
BOYS: 99th percentile cut-points

AGE	BMI
5	20.1
6	21.6
7	23.6
8	25.6
9	27.6
10	29.3
11	30.7
12	31.8
13	32.6
14	33.2
15	33.6
16	33.9
17	34.4

From National Initiative for Children's Healthcare Quality (www.nichq.org)

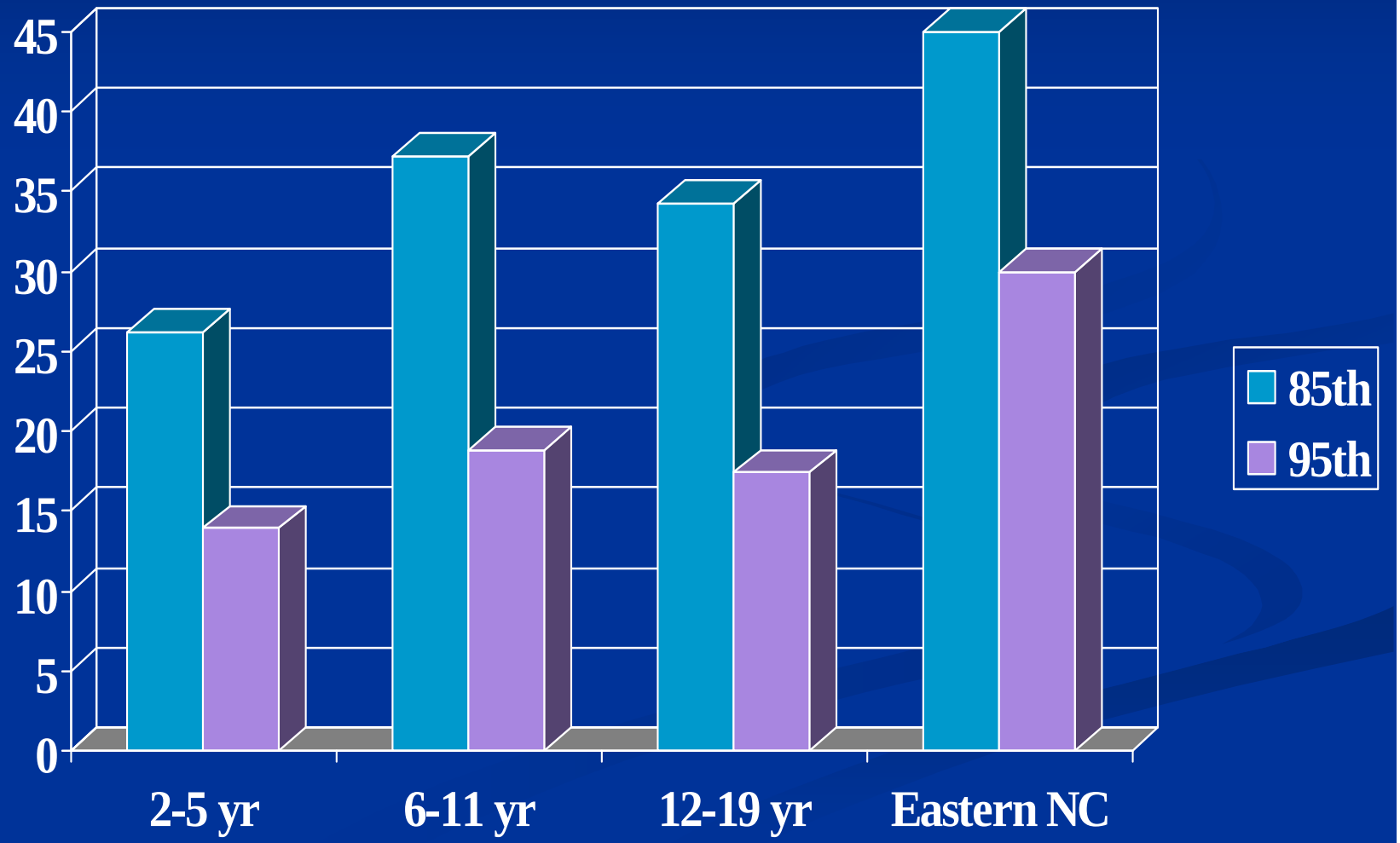
Prevalence of Overweight by Era and Age

(data from various NHES and NHANES, BMI ≥ 95th tile)



Prevalence of At-Risk and Overweight

(NHANES 2003-2004 vs. Eastern NC)

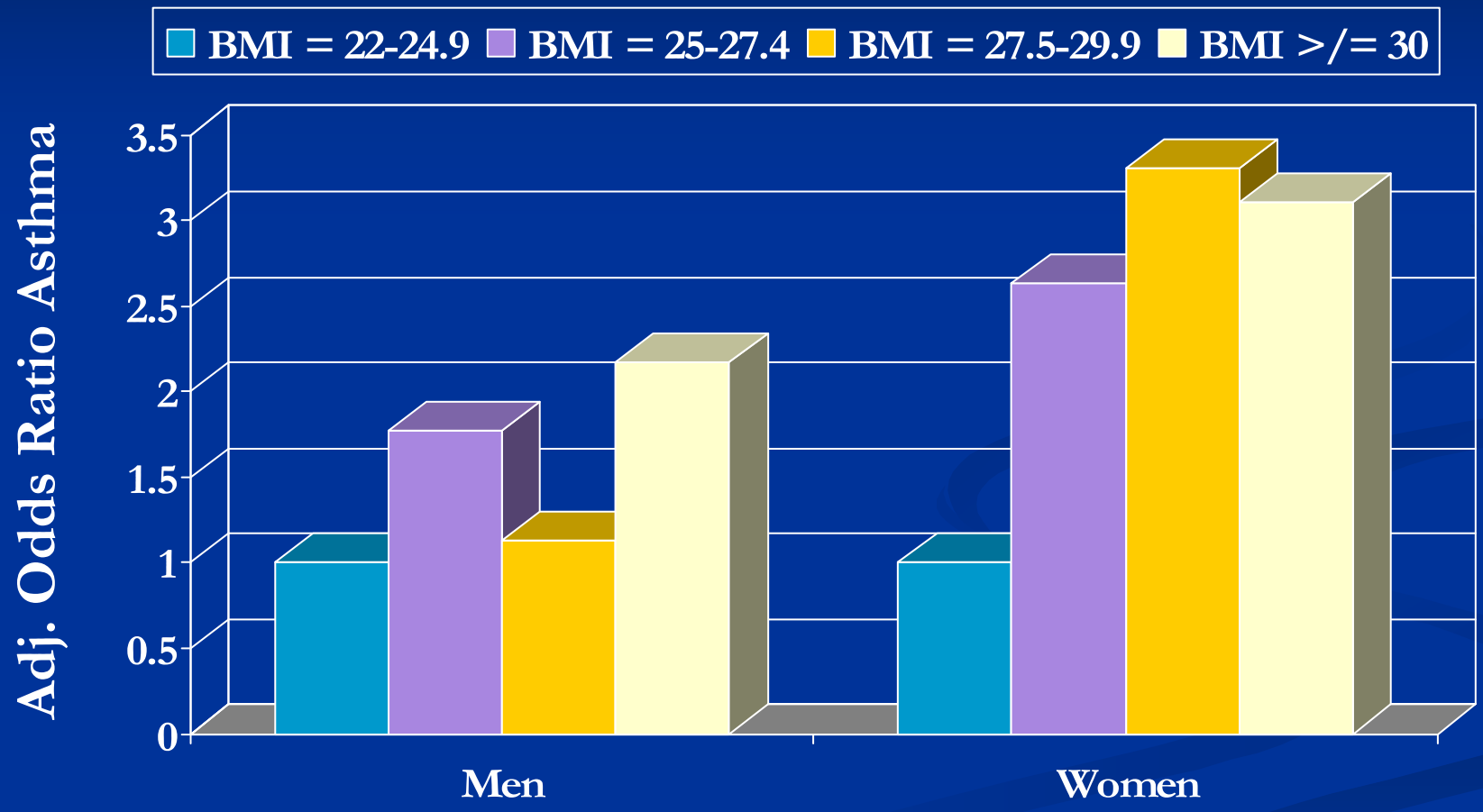


What is the evidence that obesity and asthma are related?

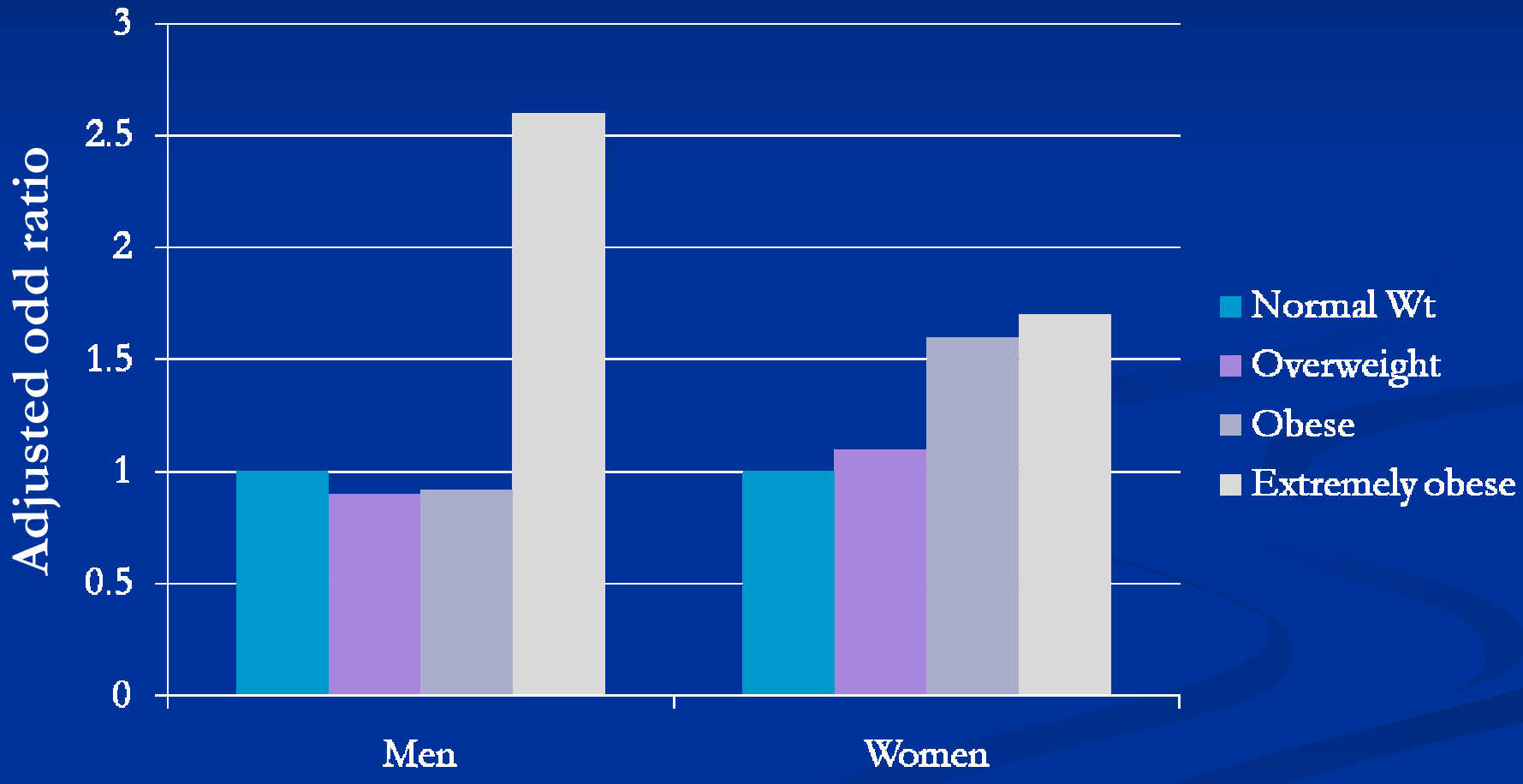
"Fast food comes to the plains"

Body Mass Index and the risk of asthma in adults: A cross-sectional study (n 5,524)

Luder E, et al. *Resp Med* 2003;98:29-37



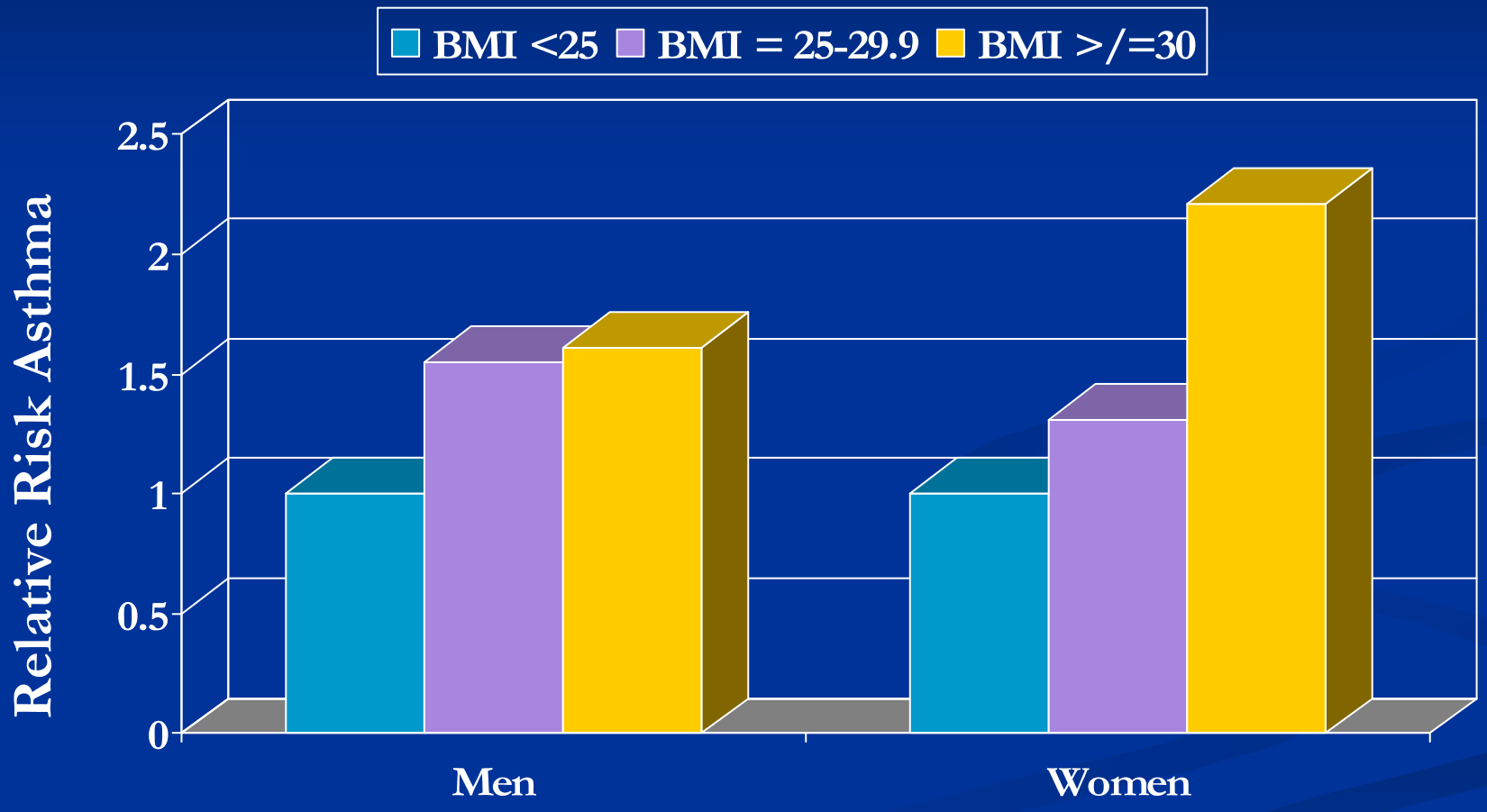
Association between asthma and weight status in US adults (NHANES 2001-2004)



McHugh JM et al., Journal of Asthma, 46:759–766, 2009

Body Mass Index and the risk of future asthma in adults: A prospective study (n 135,000)

Nystad, W. *et al. Am. J. Epidemiol.* 2004 160:969-976; doi:10.1093/aje/kwh303

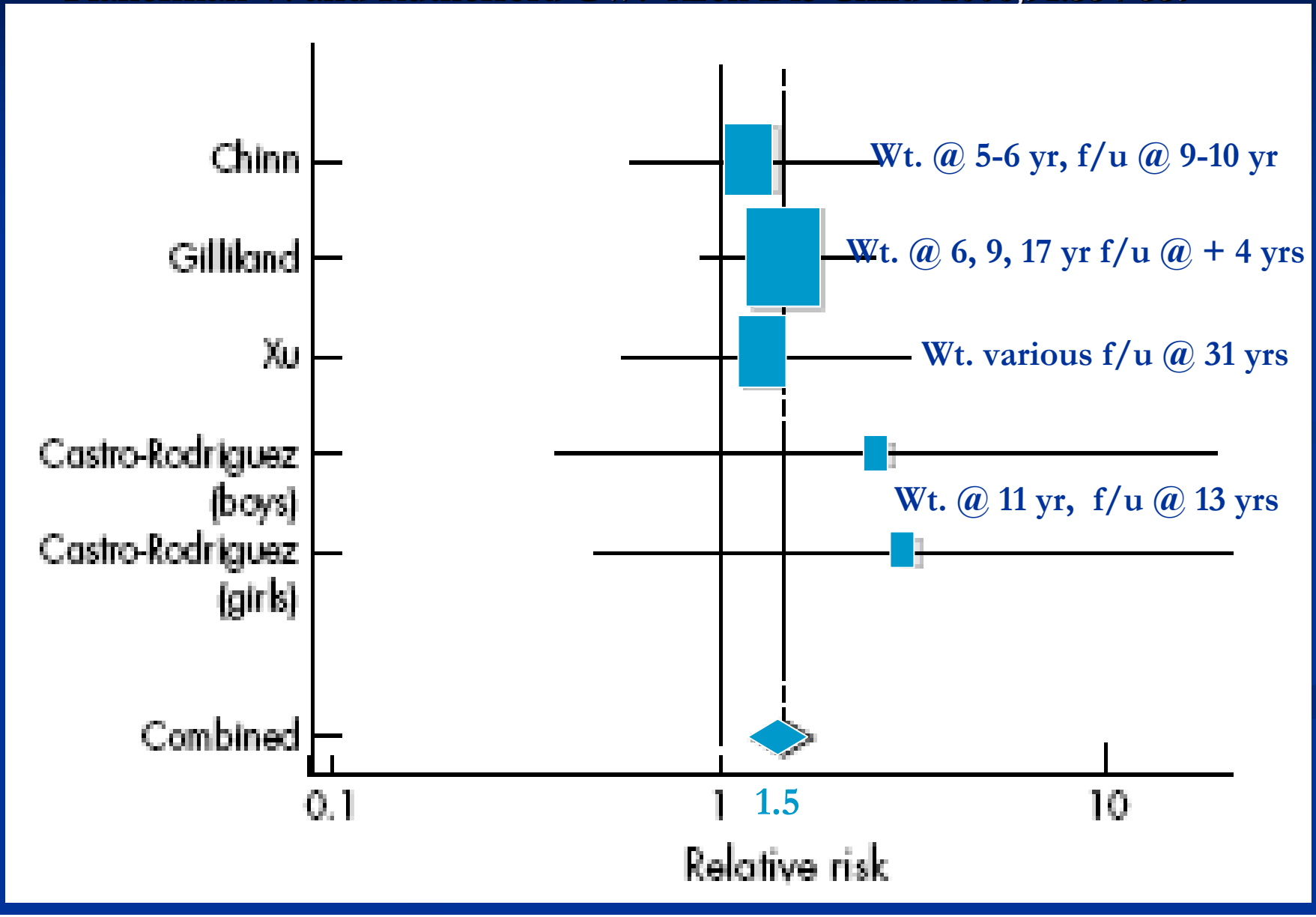


Summary: obesity and asthma in adults

- **Cross sectional studies:**
  - Most but not all support relationship
    - Risk ≈ 2-3 x higher in obese adults
  - Cannot determine cause and effect
- **Prospective studies:**
  - 7/8 support relationship
    - Risk ≈ 1.5 - 2 x higher in obese adults
  - Obesity precedes asthma – supports causative role
  - > 25 kg wt. gain after age 18 = 4.7 relative risk asthma vs. weight stable
- **Bronchial hyper-responsiveness** (response to methacholine) increases with BMI
  - N = 11,277 subjects (Chinn S. et al. Thorax 2002;57;1028-33).

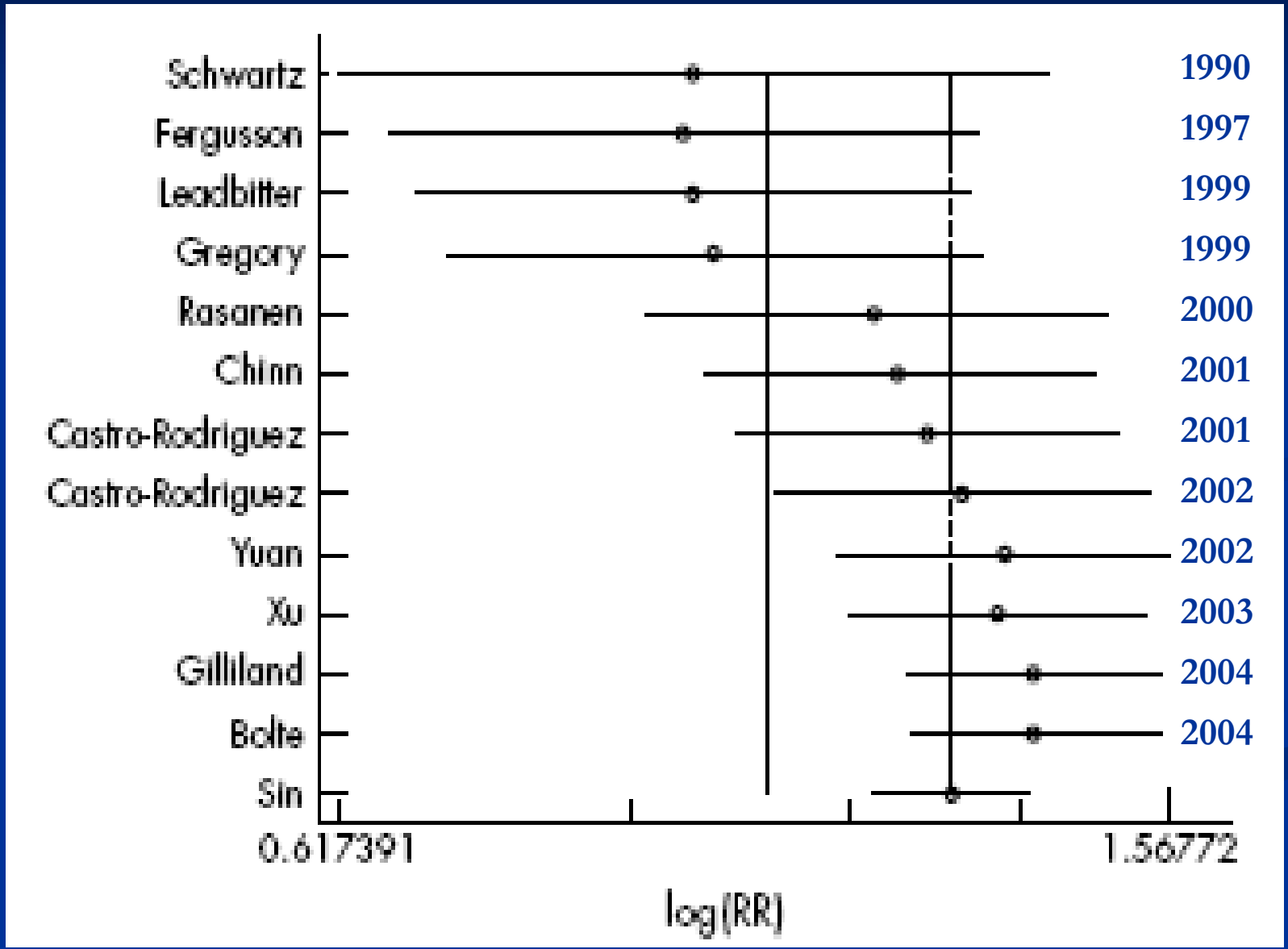
Overweight in school age and risk future asthma: Prospective studies (n 15,703)

Flaherman V. and Rutherford GW. *Arch Dis Child* 2006;91:334-339



Childhood weight and relative risk future asthma (by year)

Flaherman V. and Rutherford GW. *Arch Dis Child* 2006;91:334-339

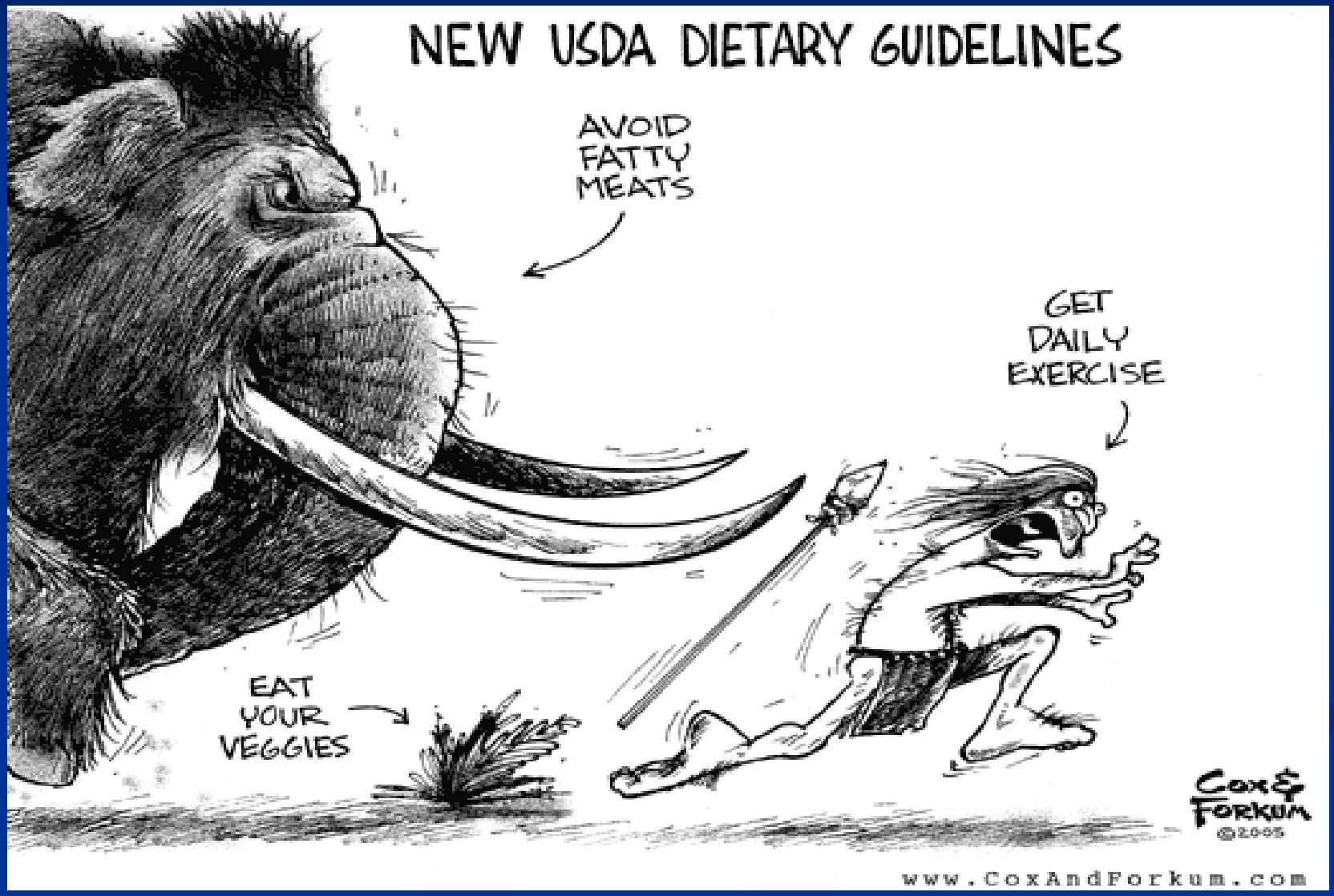


Childhood obesity and subsequent asthma

Flaherman V. and Rutherford GW. *Arch Dis Child* 2006;91:334-339

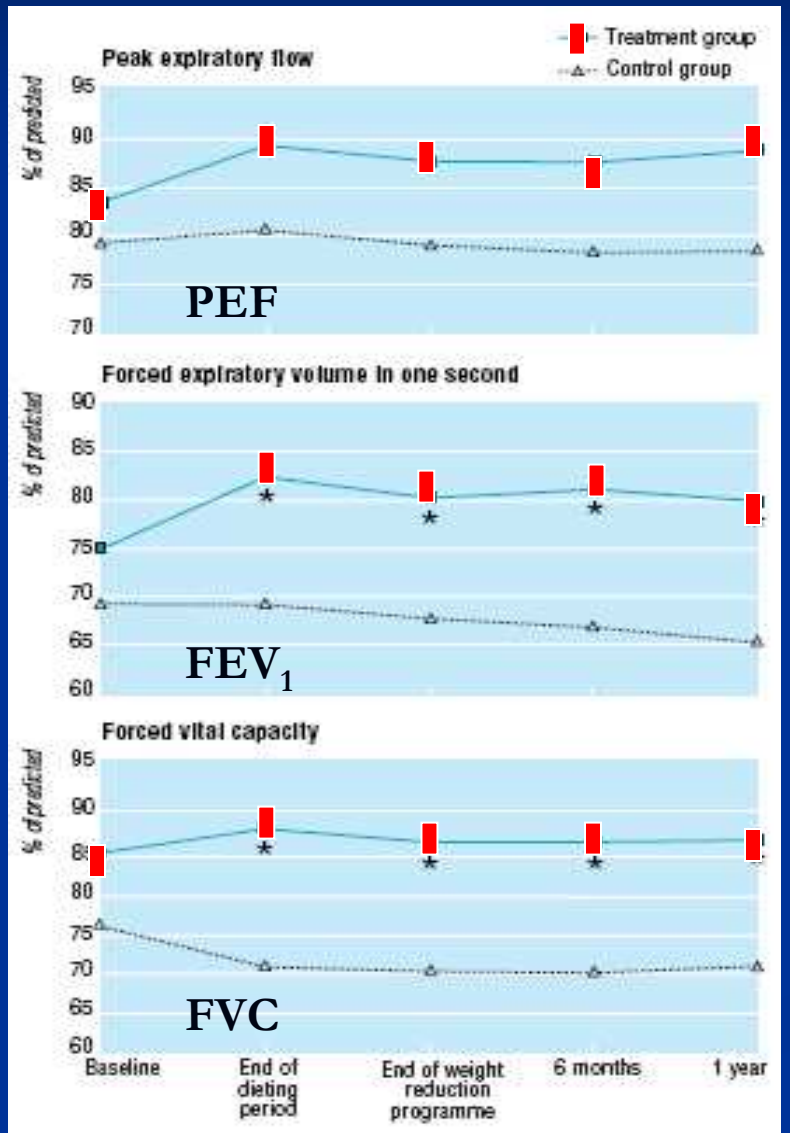
- High body weight in school aged children
  - Increases risk of future asthma by 50%
  - Responsible for ≈ 6.6% of childhood asthma
  - Causes >100,000 cases childhood asthma in US
- High birth weight
  - Increases risk of future asthma by 20%
- Maternal pre-pregnancy BMI ≥ 30?
  - Offspring have 52% higher odds of asthma at age 3
    - Reichman NE, Nepomnyaschy L. *Matern Child Health J.* 2008;12:725-33

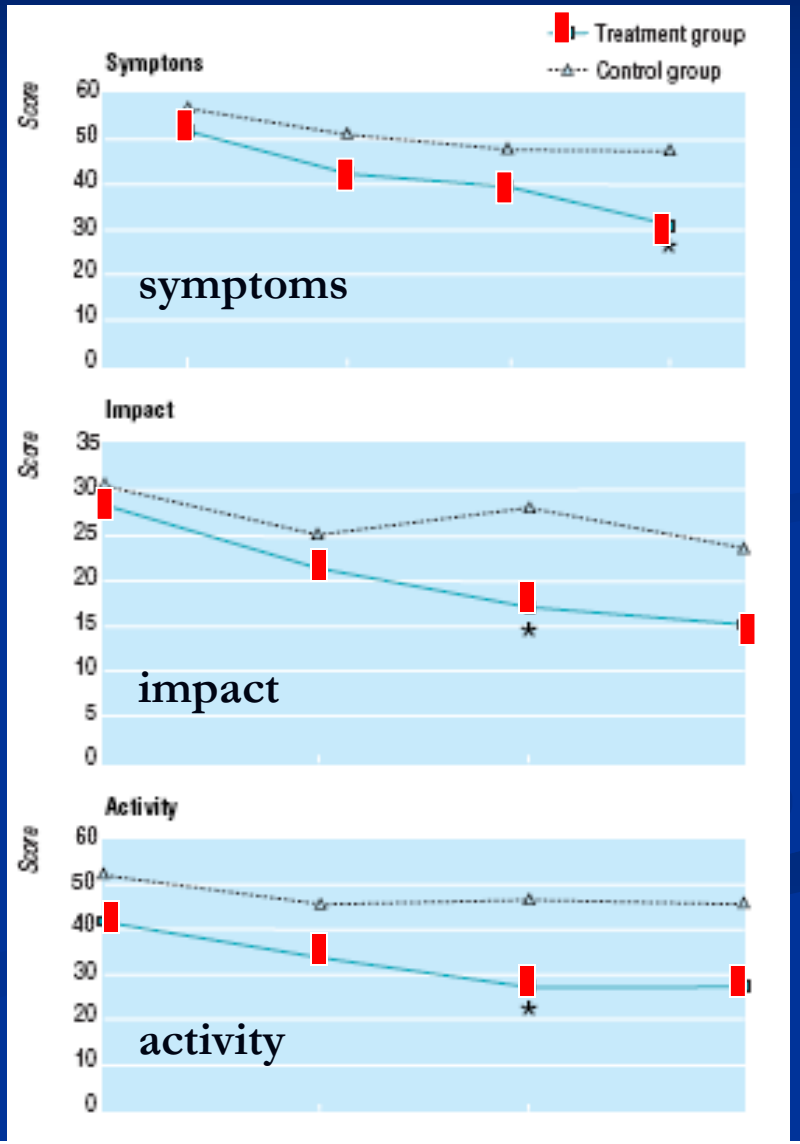
If obesity causes asthma will weight loss treat it?



Weight loss (14.5%) with VLC diet improves asthma in obese adults (BMI 30-42)

Stenius-Aarniala et al BMJ 2000;320:827





Weight loss associated with gastric banding improves asthma in obese women

Maniscalco M et al. Resp Med 2008;102:102-108

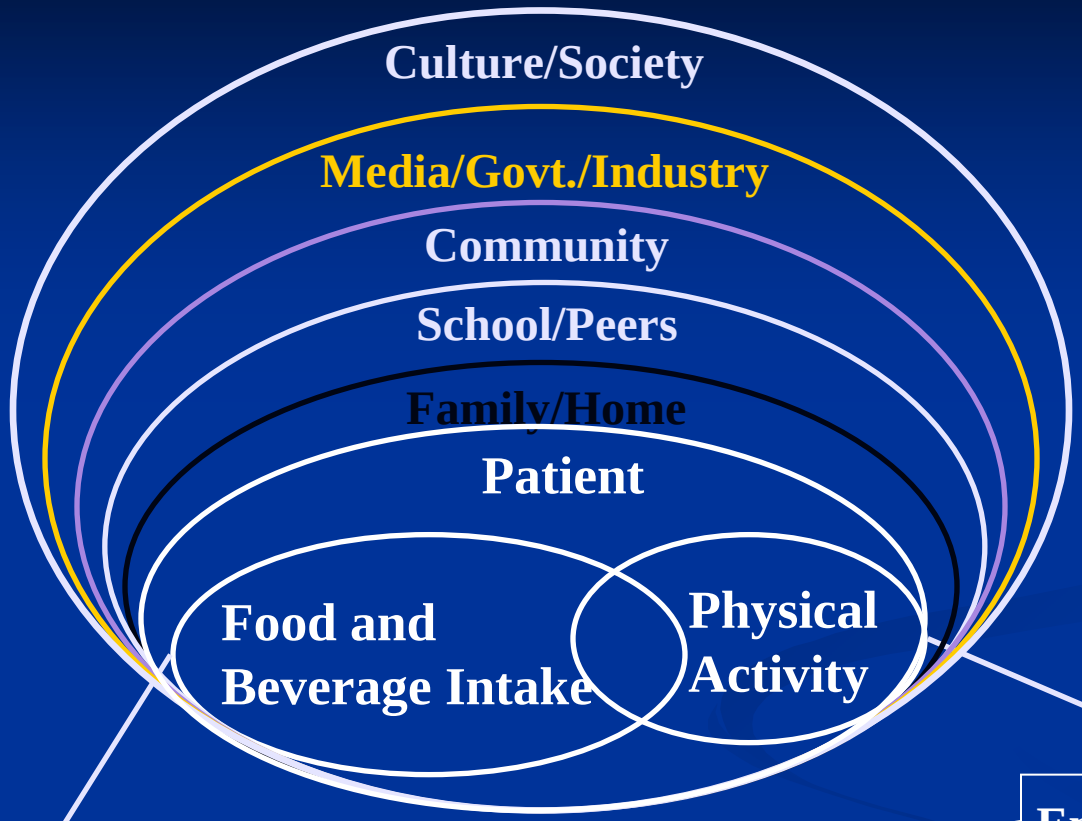
	Surgery Group		Control Group	
	baseline	1 yr F/U	baseline	1 yr F/U
Weight kg	115	89	113	118
BMI	45.2	34.8	44	45.3
ACT score	18.7	22.2	18.8	18.6
FEV_1 L	83.0	87.2	82.3	84.5
FVC L	87.8	95.2	87.1	86.1

* Only parameter that does not show significant change with gastric banding

Picture from: Geoff Price "Understanding Capitalism Part IV: Capitalism, Culture and Society" Feb 4, 2005 @ rationalrevolution.net

Ecological Systems Theory Model

Davison KK, Birch LL *Obes Rev* 2001;2:159-71



Energy Intake

Essential calories

Discretionary calories

Energy Expenditure

Basal metabolism

Processing food

Maintenance/repair

Growth

Physical activity

Genetic factors

Epigenetic/Metabolic factors

Feed-Forward Model for Obesity

Proteins Secreted by Adipose Tissue and Their Influence on Insulin Sensitivity

Lazar M. Science 2005;307:373-5

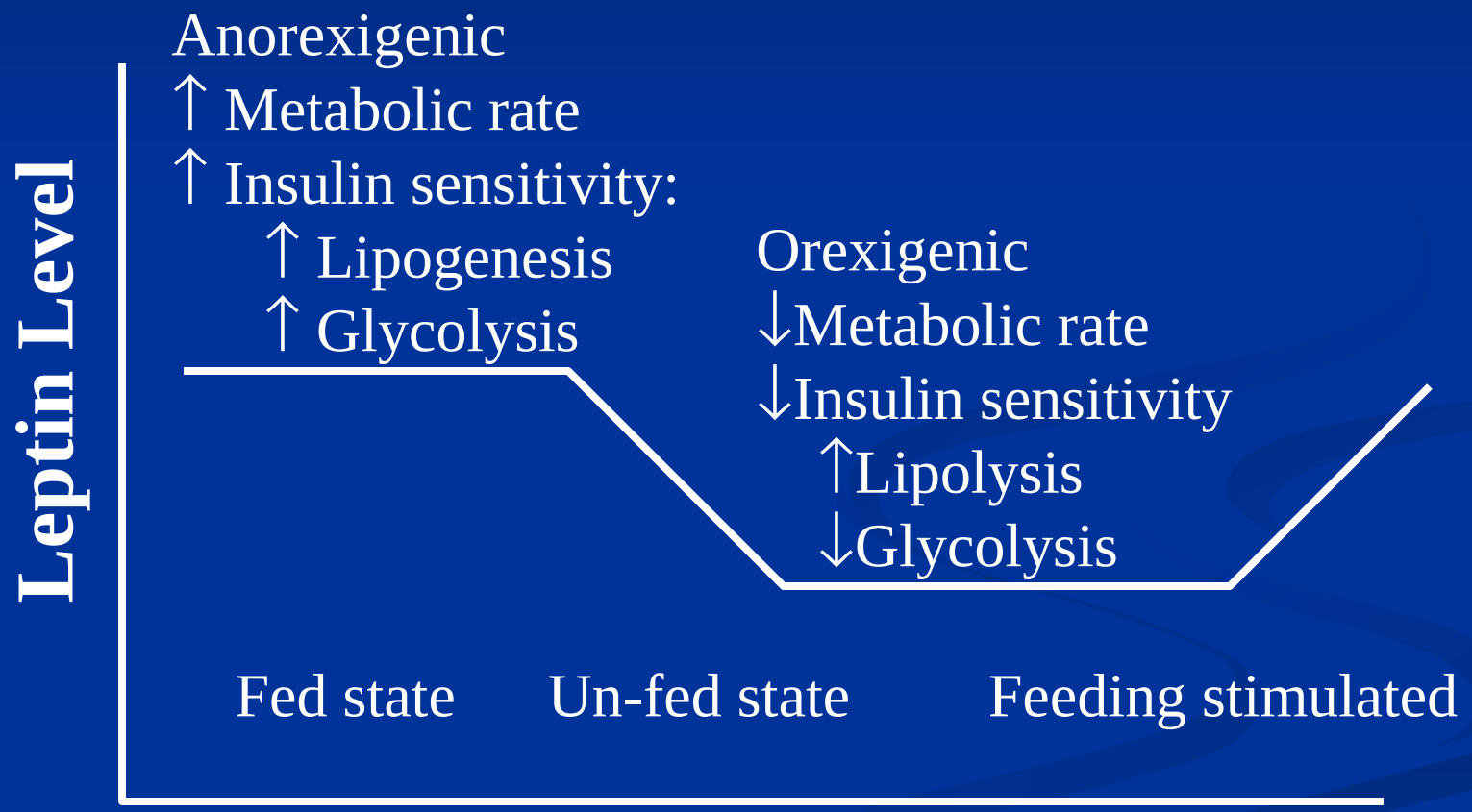
Adipose-derived prot.	Effect on Insulin sen.	Other sources/actions?
Leptin	**Improvement**	**Adipose specific** **Pro-inflammatory**
Adiponectin	**Improvement**	**Adipose specific** **Anti -inflammatory**
Adipsin/ASP	Decline	Adipose specific
Resistin	Decline	Macrophage
TNF-α	Decline	Macrophage
IL-6	Decline	Macrophage
MCP-1	Decline	Macrophage
Visfatin (PBEF)	Improvement	Liver/Lymphocytes
PAI-1	Decline	Liver
Angiotensinogen	Decline	Liver

Leptin

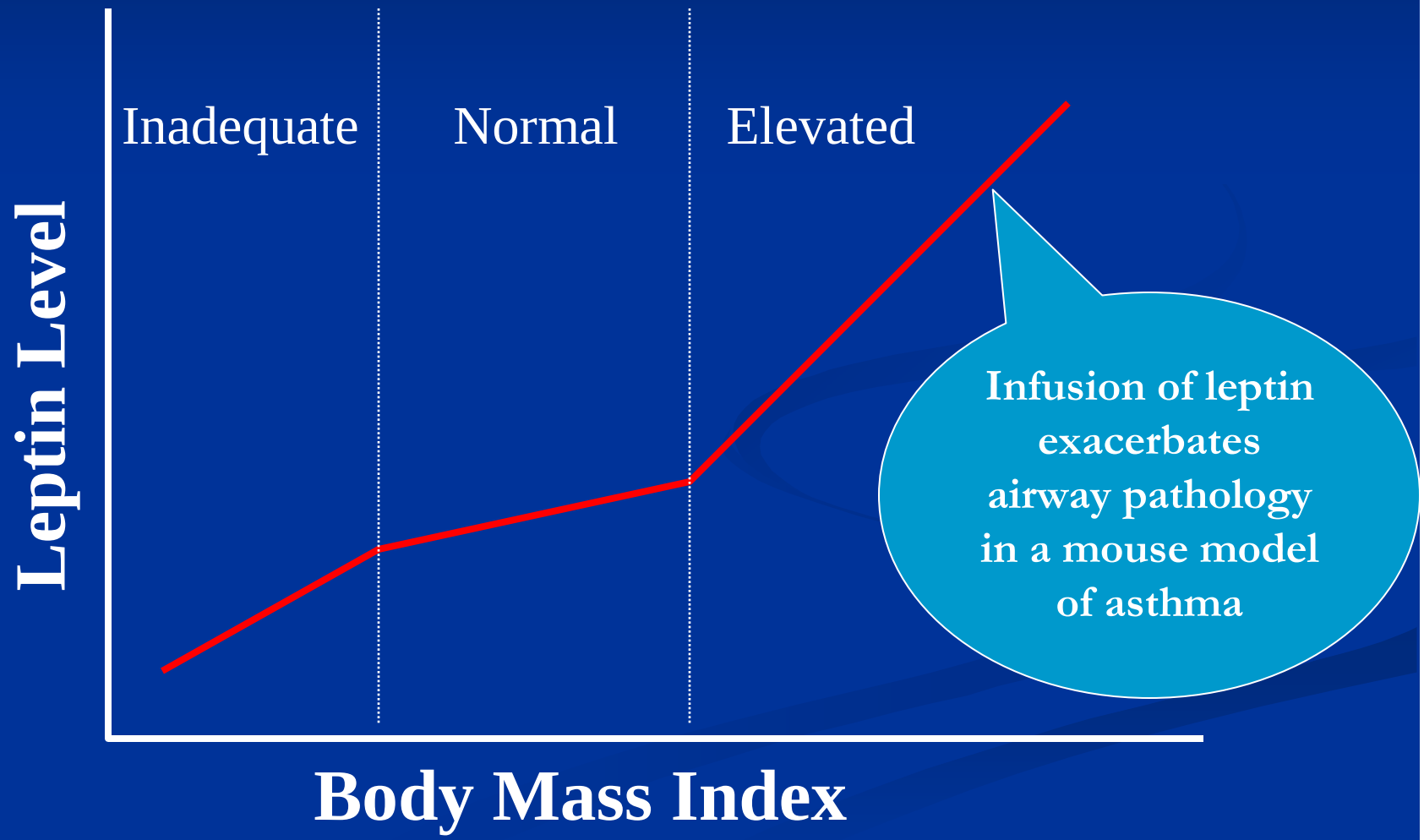
- Produced almost exclusively in adipose tissue
- Levels reflect energy stores
  - Promotes satiety – targets hypothalmus
  - Accelerates metabolism
  - Required for menstruation
- Promotes insulin sensitivity

- Up-regulates leukotriene synthesis

Leptin Modulates Energy State and Feeding Behavior

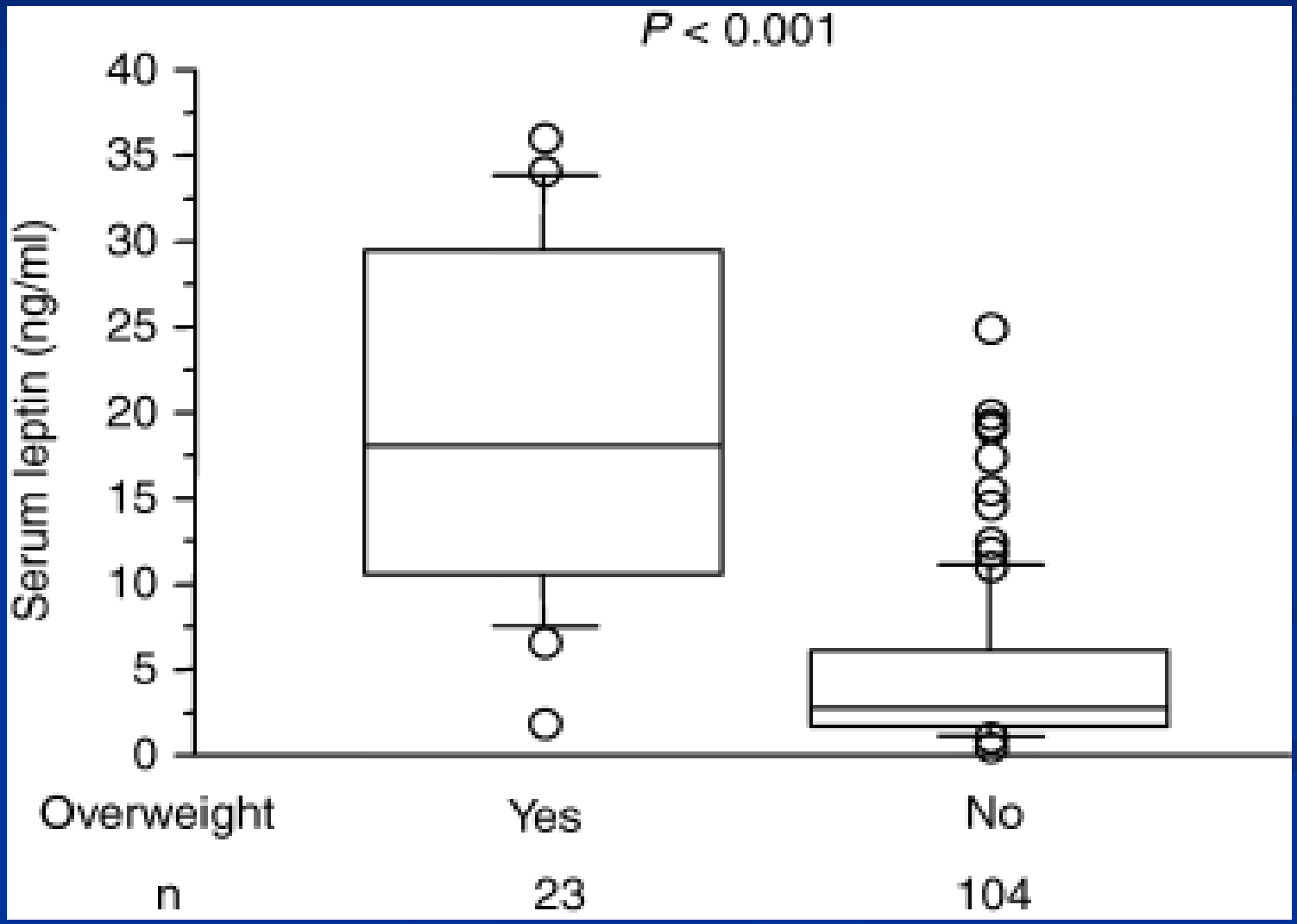


Leptin Levels are Related to Fat Mass



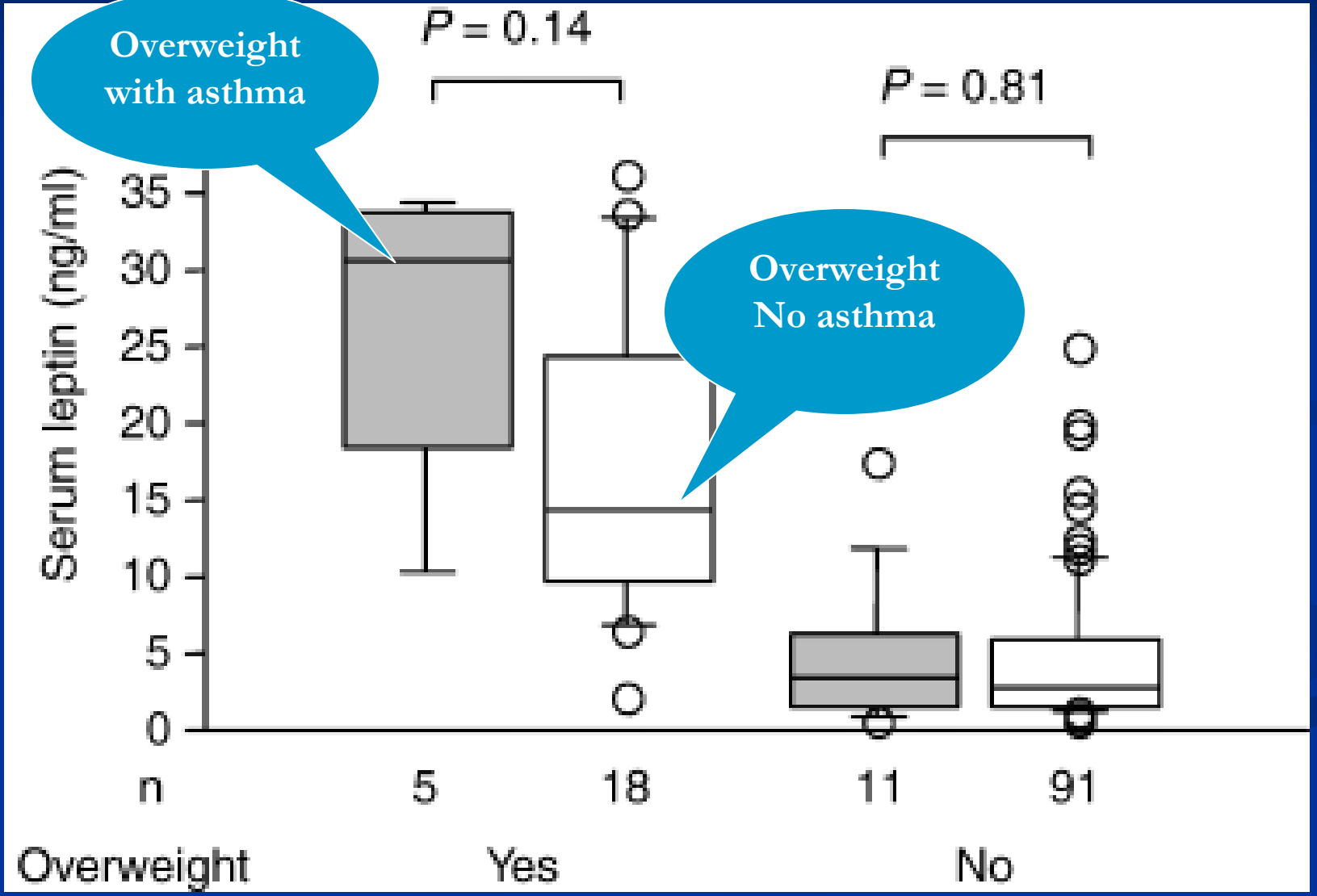
Leptin levels and weight status in 12 year olds

Mai, Bottcher, Leijon Pediatr Allergy Immunol 2004;15:523-530

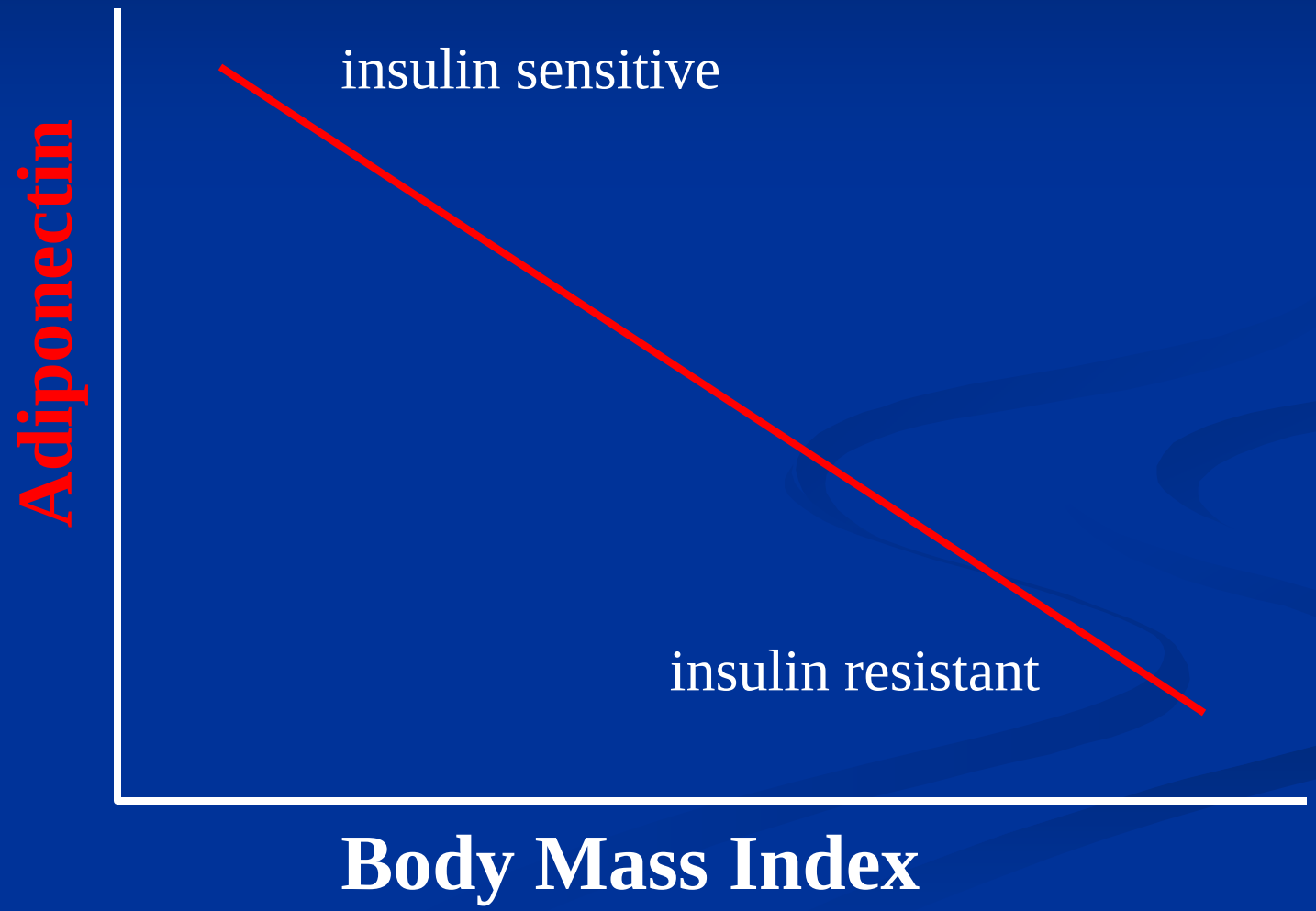


Leptin levels are higher in overweight 12 year olds with asthma than overweight non-asthmatics

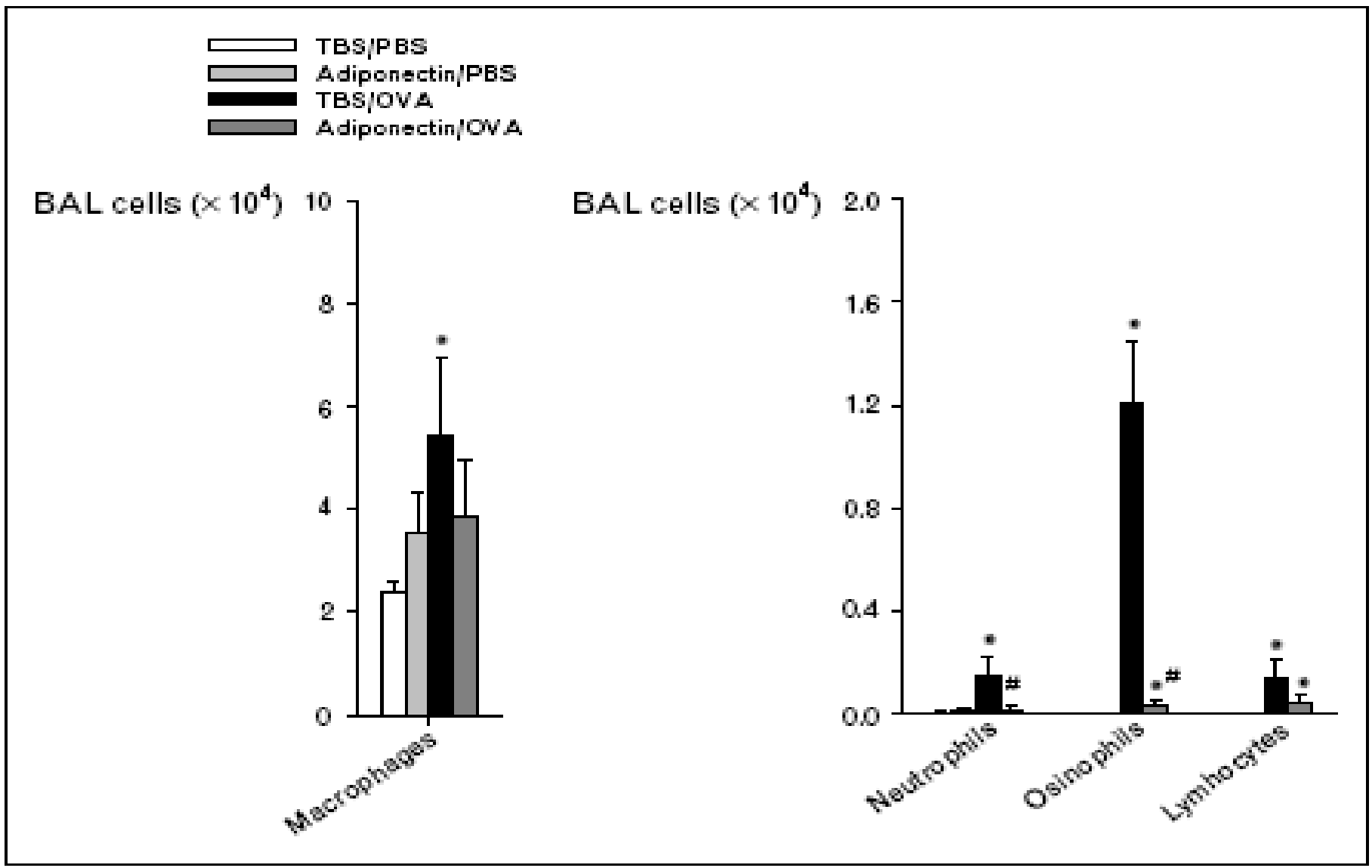
Mai, Bottcher, Leijon Pediatr Allergy Immunol 2004;15:523-530



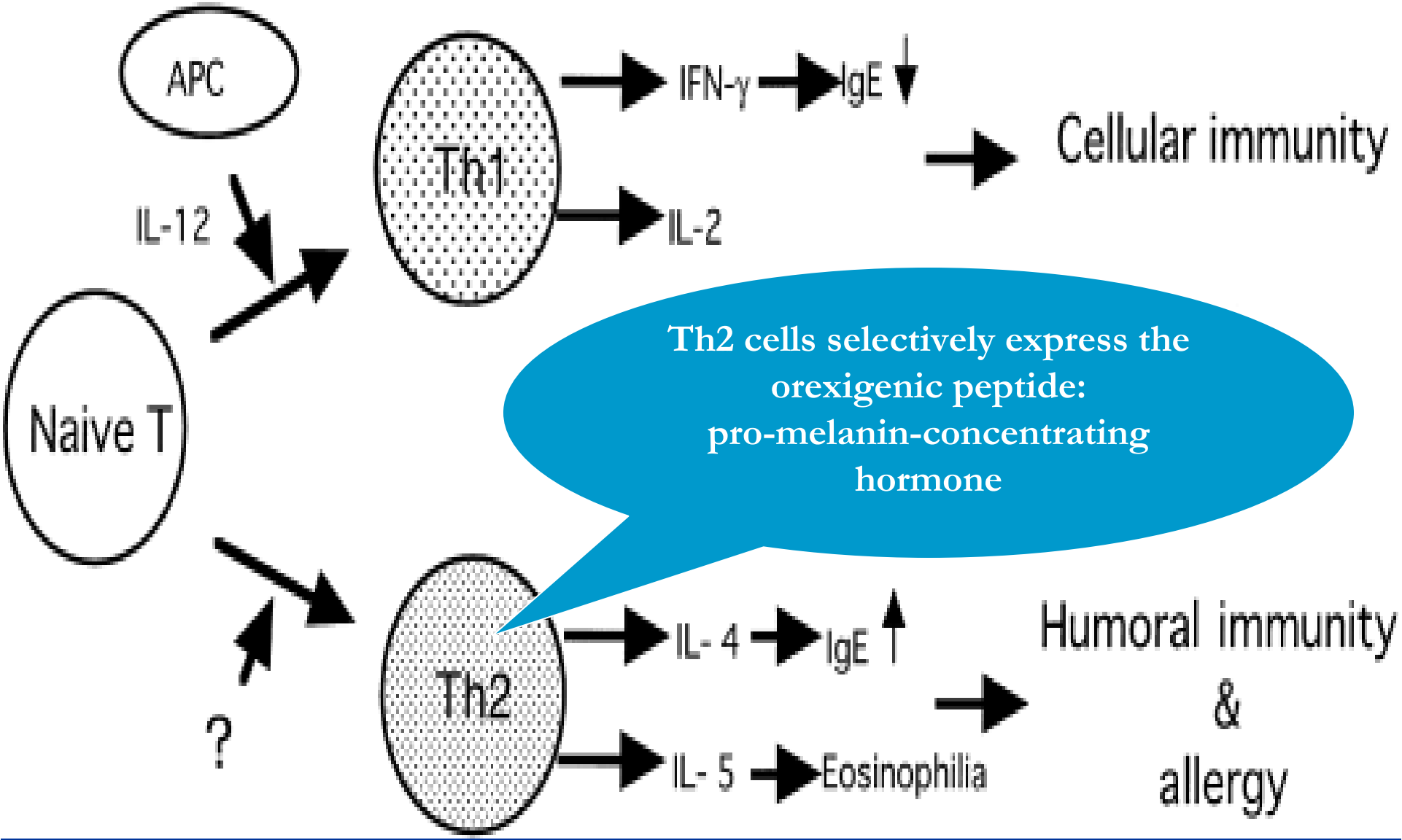
Adiponectin Levels and Fat Mass are Inversely Related



Infusion of adiponectin attenuates pathological immune response in mouse model of asthma



Th2 predominance results in atopy and asthma



MC4R defect example of effects of PMCH pathway's influence on obesity

Farooqi and O'Rahilly

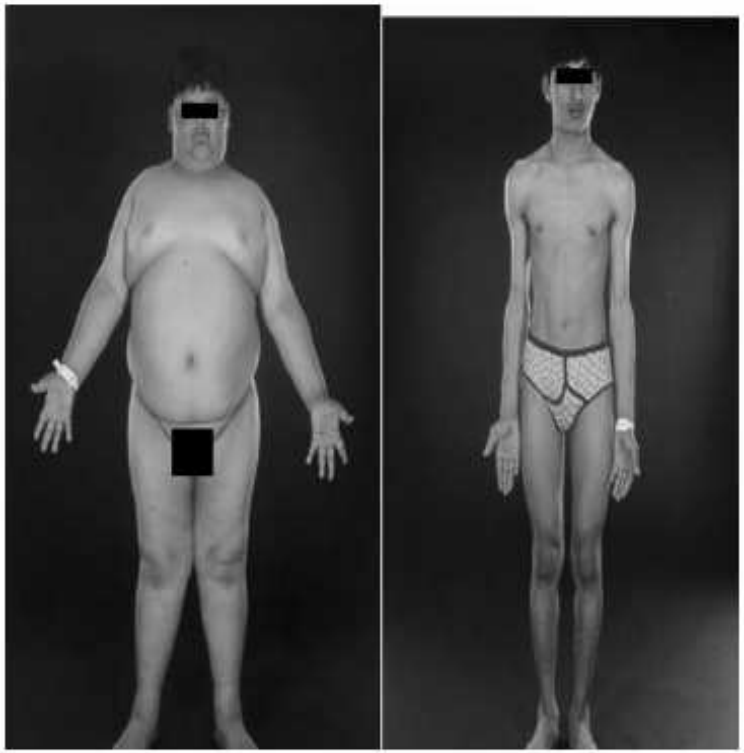
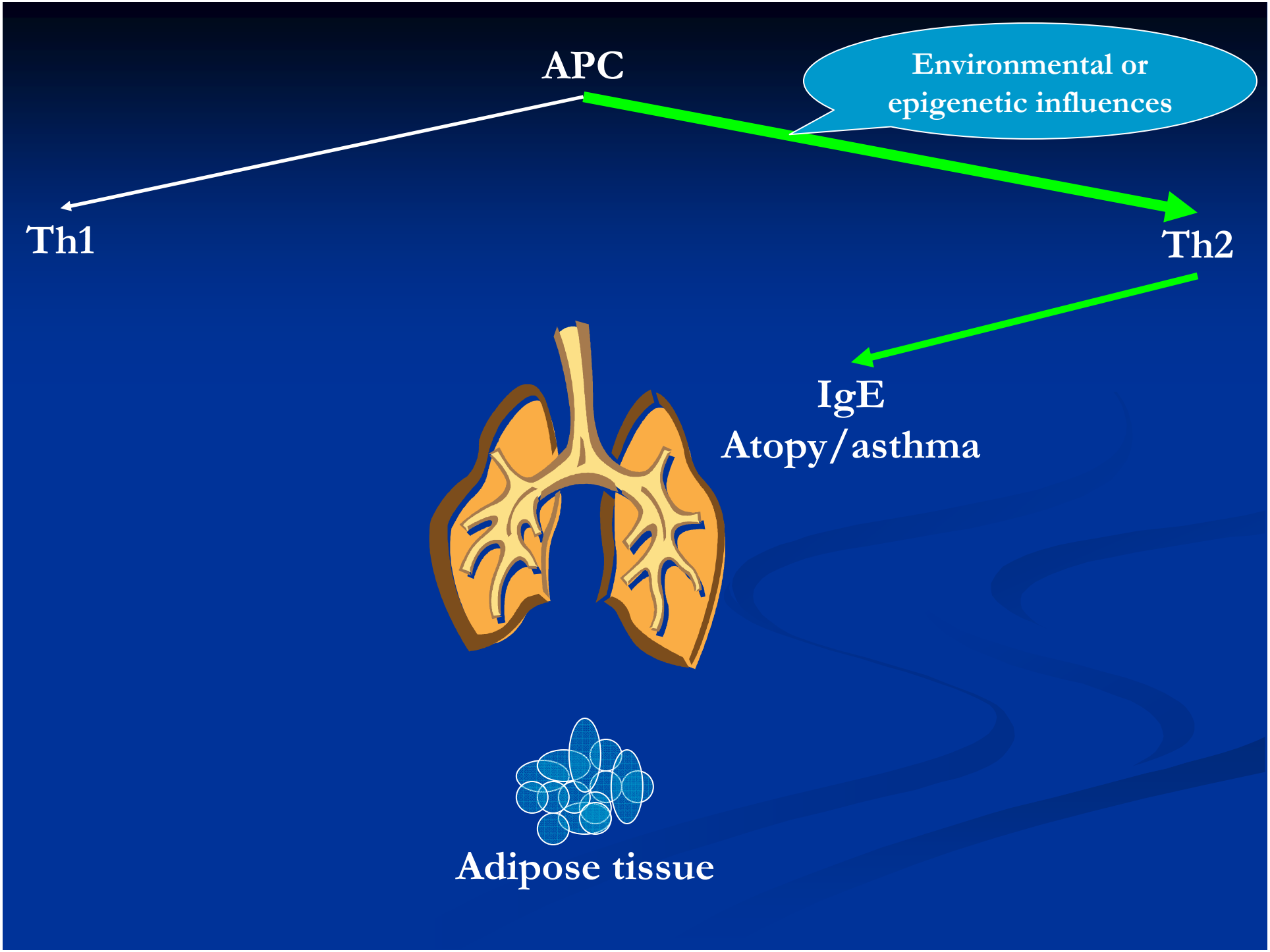
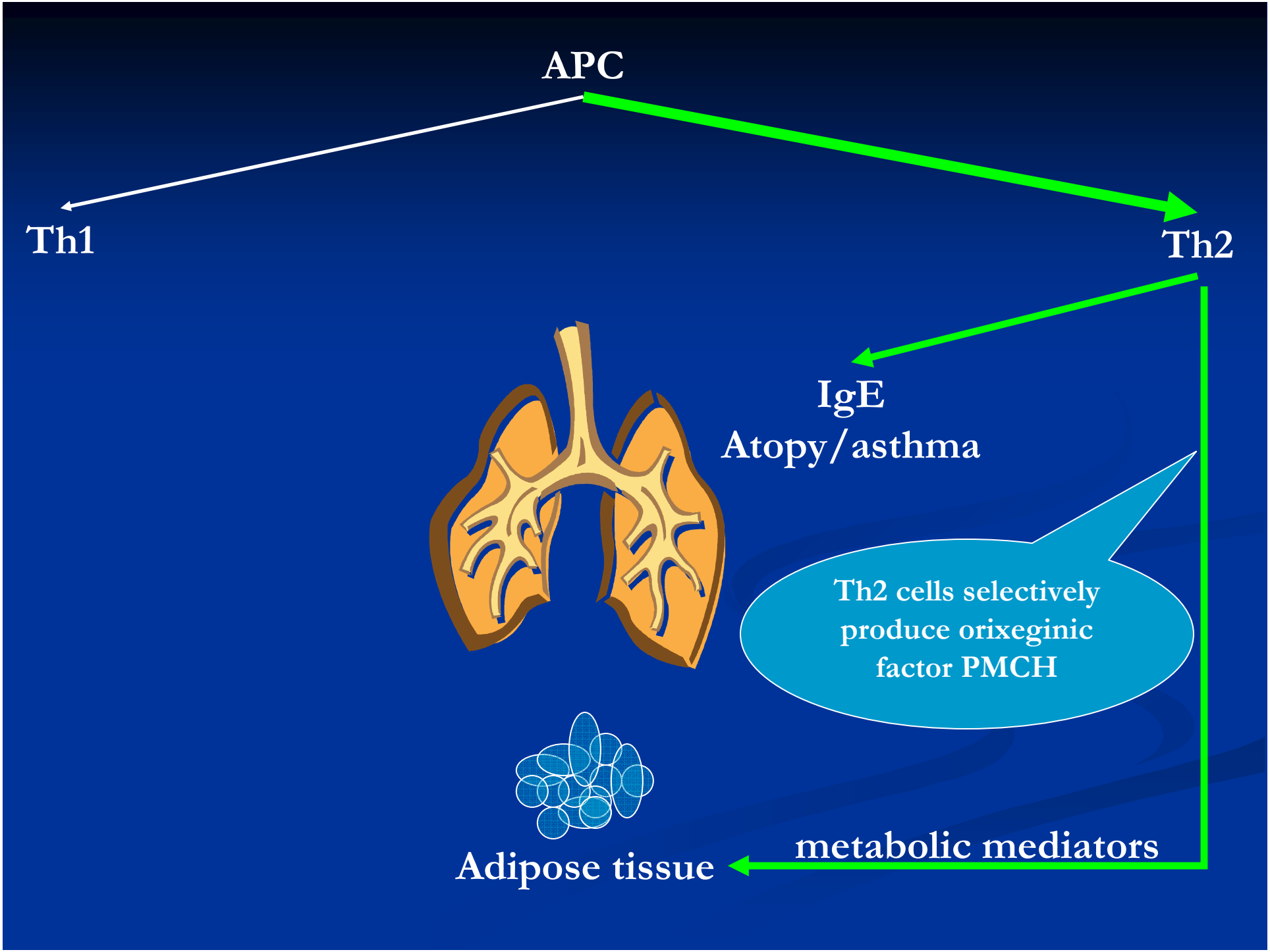
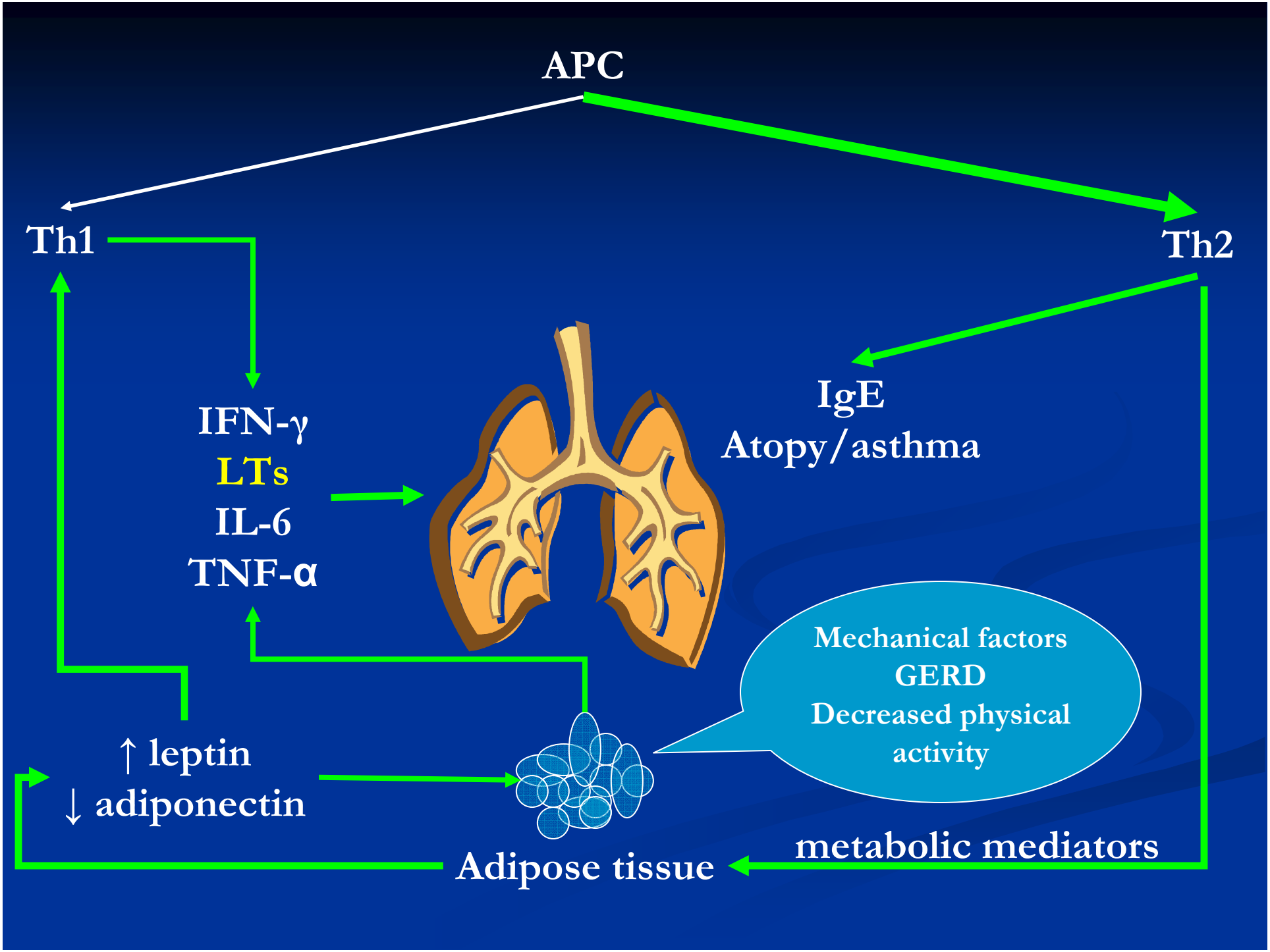


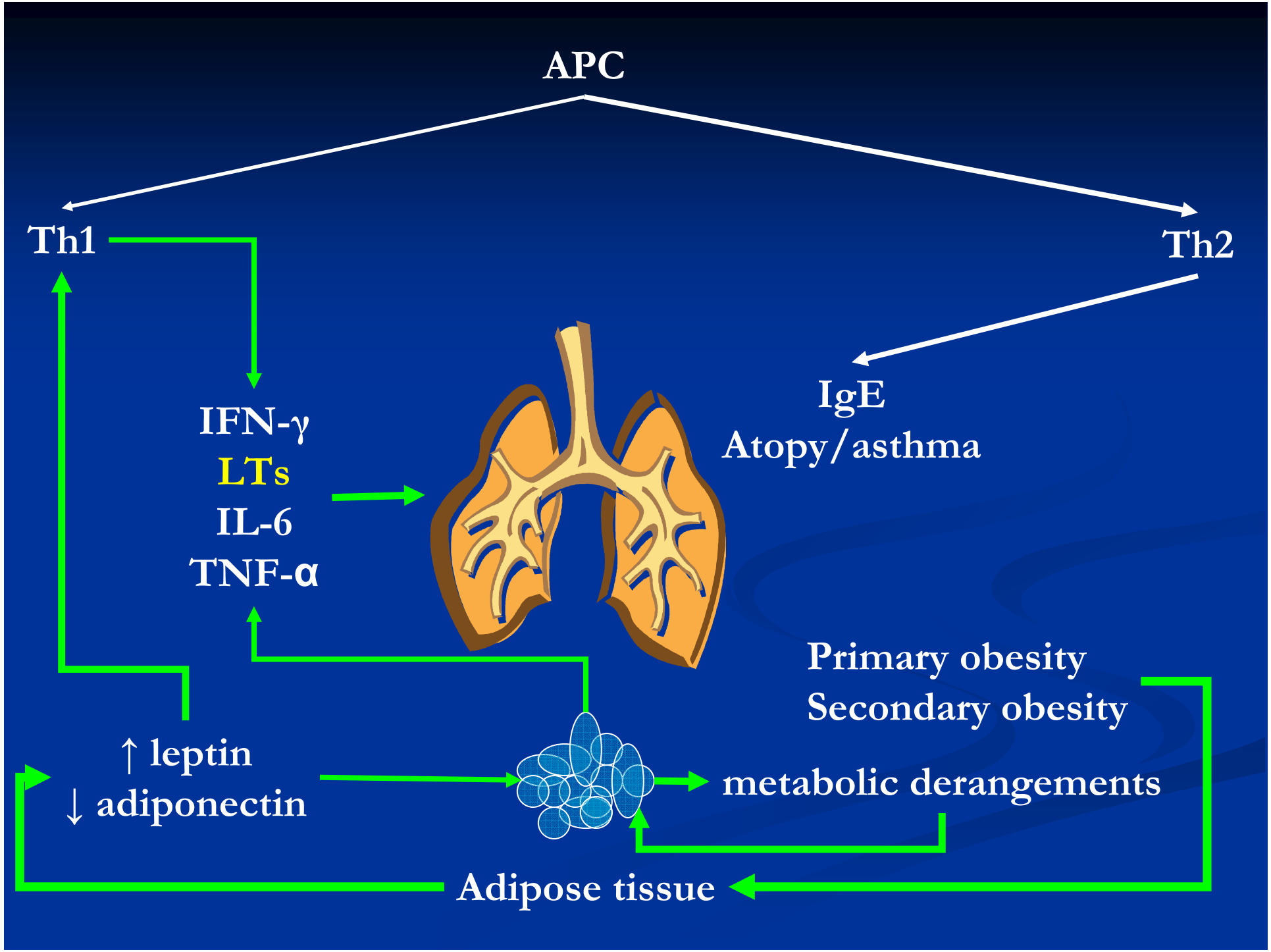
Figure 3 Clinical phenotype of MC4R deficiency. MC4R mutations result in a dominantly inherited obesity syndrome. *Left*: 9-year-old with MC4R mutation. *Right*: 16-year-old sibling with normal MC4R.

- Loss of α-MSH mediated anorexia
- Phenotype
  - Hyperphagia
  - Accelerated linear growth
  - Increased bone density
  - ↑adipose and lean tissue mass
- Multiple alleles
  - Codominant
  - Homozygous > heterozygous
- Prevalence
  - ≈ 6% in severe childhood onset obesity
  - 1/2000 general population


APC
Environmental or epigenetic influences
Th1
Th2
IgE
Atopy/asthma
Adipose tissue

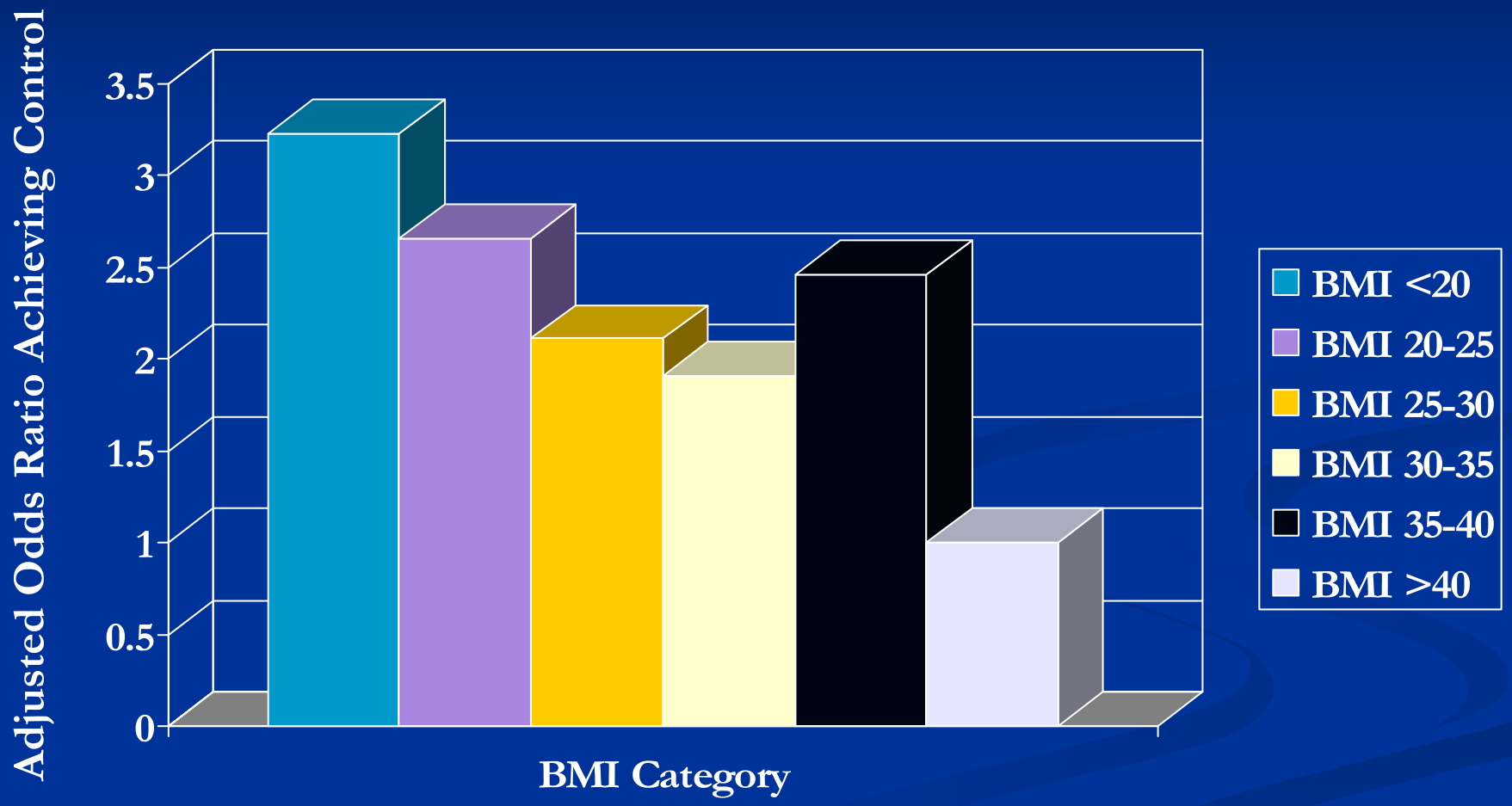

APC
Th1
Th2
IgE
Atopy/asthma
Th2 cells selectively produce orixeginic factor PMCH
metabolic mediators
Adipose tissue


APC
Th1
Th2
IFN-γ
LTs
IL-6
TNF-α
IgE
Atopy/asthma
Mechanical factors
GERD
Decreased physical activity
↑ leptin
↓ adiponectin
Adipose tissue
metabolic mediators


APC
Th1
Th2
IFN-γ
LTs
IL-6
TNF-α
IgE
Atopy/asthma
Primary obesity
Secondary obesity
↑ leptin
↓ adiponectin
metabolic derangements
Adipose tissue

BMI influences odds of achieving good asthma control with ICS +/- LABA

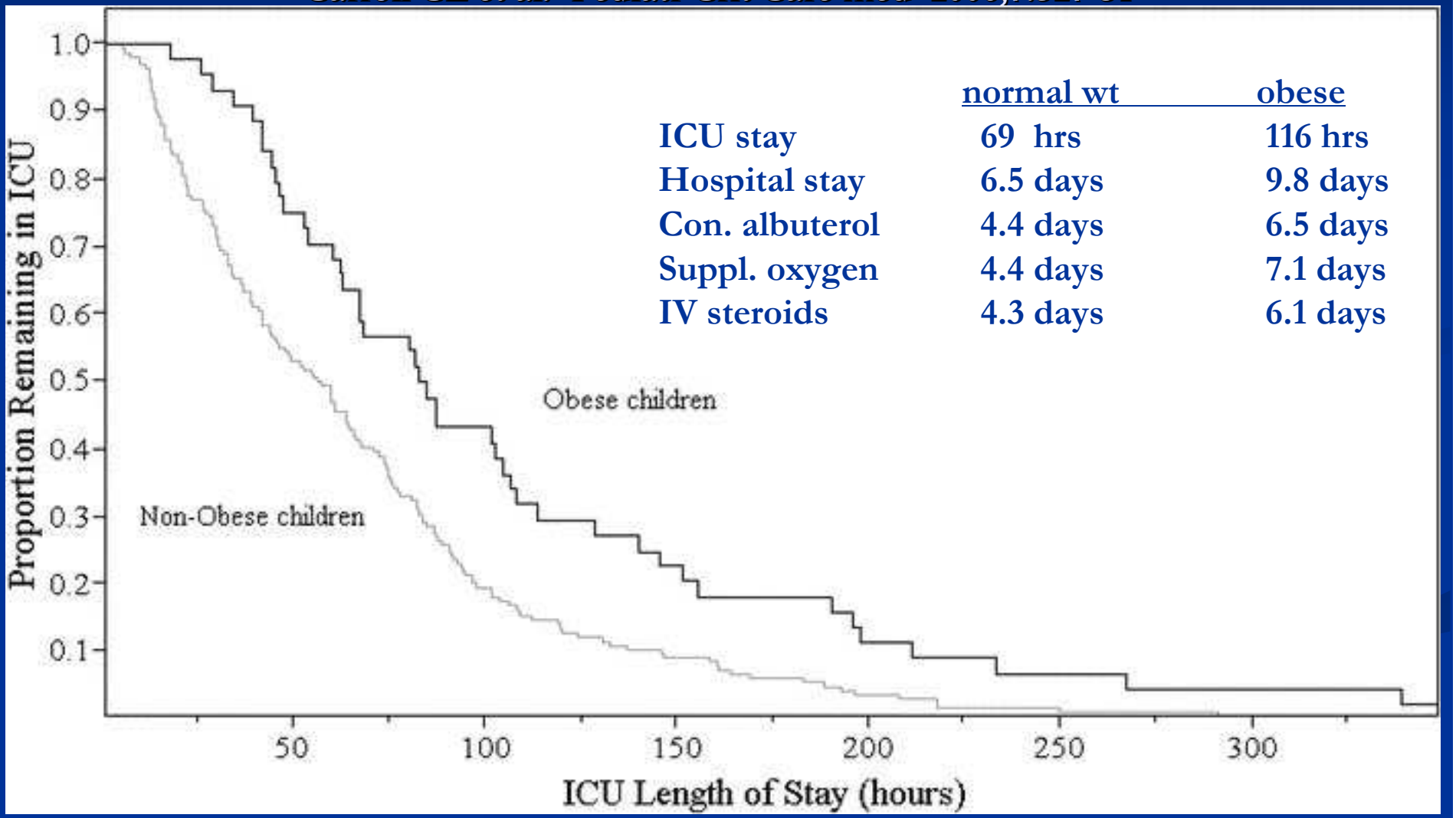
Boulet LP, Franssen E. Resp Med 2007;101:2240-2247



Obesity and response to therapy: Duration of therapy during severe asthma exacerbations in children

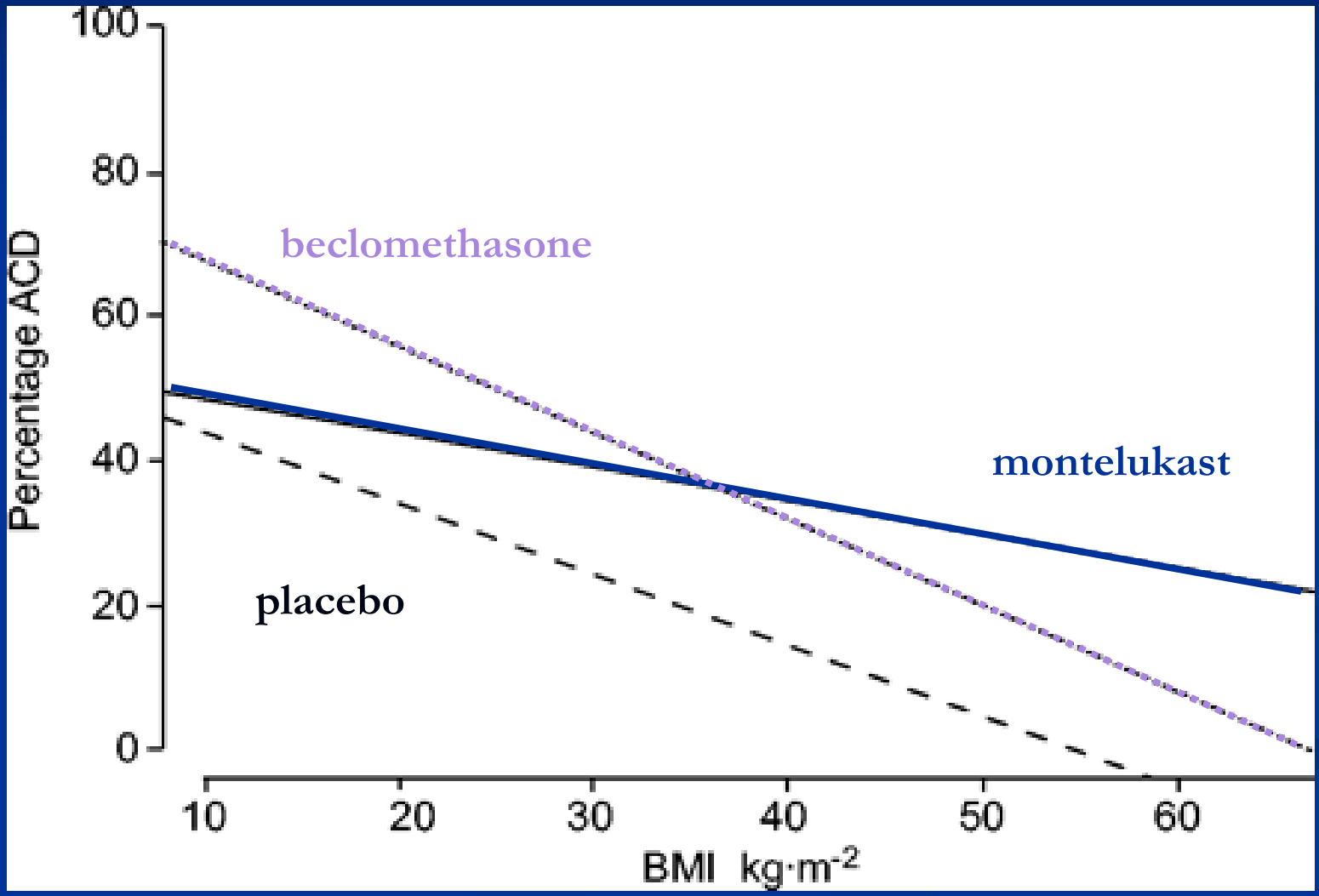
Carroll CL et al. Pediatr Crit Care med 2006;7:527-31

	normal wt	obese
ICU stay	69 hrs	116 hrs
Hospital stay	6.5 days	9.8 days
Con. albuterol	4.4 days	6.5 days
Suppl. oxygen	4.4 days	7.1 days
IV steroids	4.3 days	6.1 days



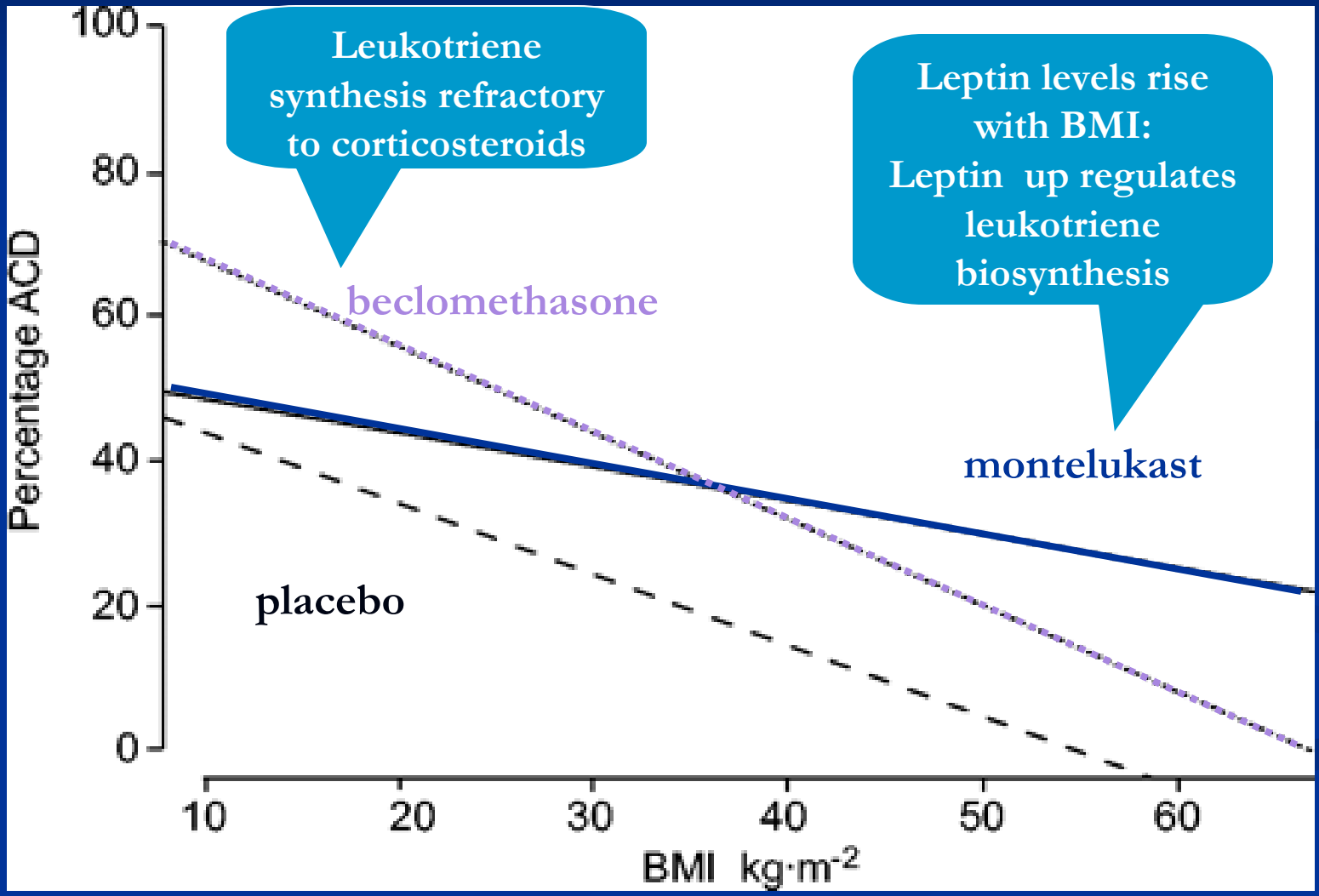
Influence of BMI on response to asthma controller agents (% asthma controlled days)

Peters-Golden, M et al. Eur Resp J 2006;27:495-503



Leptin levels may explain differential response to anti-LTs in obese asthmatics

Peters-Golden, M et al. Eur Resp J 2006;27:495-503



Conclusions

- Preponderance of evidence suggests obesity can "cause" asthma across the age spectrum
- Weight loss shown to improve asthma control in adults
- Connection between obesity and asthma likely multi-factorial
- Obese adults and children likely to be less responsive to standard treatments
  - Consider anti-LT such as moneleukast since leptin up-regulates LT production
  - Consider thiazolidinedione (TZD) as they up-regulate adiponectin production
  - Specific clinical trials currently lacking

Morbid Obesity due to Leptin Signaling Defects

Ob^{-}/Ob^{-} leptin deficient

LRb T1138S
leptin receptor defect

Leptin Deficits

Farooqi and O'Rahilly

- Leptin deficiency
  - Early onset morbid obesity
  - High fat mass
  - Infertility
  - T-cell defects recurrent infections
  - Rare: autosomal recessive
  - Readily diagnosed
  - Rx with recombinant leptin
- Leptin receptor deficiency
  - Milder phenotype
  - No specific Rx

TNF-α Levels (and other cytokines) Rise With Adiposity

TNF-α Inhibits Insulin Signaling via Suppression of Adiponectin and Induction of SOCS-3